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EPIDEMIOLOGY OF CHRONIC RESPIRATORY DISEASE: A
LITERATURE REVIEW

MICHIGAN UNIVERSITY

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OF
CHRONIC RESPIRATORY DISEASE:
A LITERATURE REVIEW**

by

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ABSTRACT

This review of published studies pertaining to the epidemiology of chronic respiratory disease focuses on three disorders -- asthma, chronic bronchitis, and emphysema. Particular emphasis is directed toward the latter two maladies. Chronic lung diseases either cause or contribute to an increasing number of deaths throughout the world. Practical measures for identifying persons who have chronic respiratory disease, particularly through the use of standardized questionnaires, are described. The review cites studies from several countries that explore the distribution and etiology of chronic respiratory disease, including the effect of air pollution. Most studies have confirmed the initial observation that the most important factor in the natural history of chronic respiratory disease is smoking, particularly cigarette smoking. Occupational exposure is also important with workers in dusty occupations evidencing an excess of chronic respiratory disease.

EPIDEMIOLOGY OF CHRONIC RESPIRATORY DISEASE: A LITERATURE REVIEW

INTRODUCTION

HISTORICAL BACKGROUND

The chronic respiratory diseases include chronic bronchitis, emphysema, asthma, bronchiectasis, pneumoconiosis, and chronic interstitial pneumonia. This review, however, will be chiefly concerned with the first three of these, and more with the first and second than with the third.

The term chronic bronchitis was first used in 1808 by Badham,¹ who recognized acute and chronic varieties. In 1819, Laennec² described chronic bronchitis as "pulmonary catarrh," and classified it into chronic mucous, chronic pituitous, suffocative, and dry varieties. Laennec is usually credited with the first description of emphysema, but he was actually preceded in this by Mathew Baillie,³ who in 1793 observed the disease in the lungs of Dr. Samuel Johnson. In a recent review of the early medical literature on emphysema, Rosenblatt attributes the earliest autopsy descriptions to Bonetus,⁴ Ruysch,⁵ and Floyer,⁶ in the late 17th and early 18th centuries; and notes that in 1764 Watson⁷ described the clinical features of emphysema, subsequently confirmed at autopsy, in a man who died of respiratory failure at the age of 28. The cardiac complications of chronic bronchitis were described in 1831 by Mackintosh,⁸ who noted that Morgagni and Valsalva were well acquainted with the disease.

The clinical features of chronic bronchitis and emphysema were well known to physicians in the nineteenth century.⁹⁻¹⁴ Etiological factors such as climate, weather, exposure to cold or damp, changes of temperature, and "long standing local irritation from dust or overdried air"¹³ were believed to be important. Most of these authors also considered family history to be significant and indicative of hereditary influence. In addition, they speculated on the mechanism of production of emphysema.¹²

Interest in chronic respiratory disease, particularly in chronic bronchitis, developed in Britain after the Second World War, and was stimulated significantly by the severe London fog of 1952. This interest has increased greatly and has been accompanied by a growing interest in bronchitis in many European countries. More recently, attention to the chronic respiratory diseases in the United States, Canada, and Australia has also increased. A number of excellent reviews have recently

been published, some general in scope¹⁵⁻²⁴ and others concentrating primarily on one particular aspect of the subject.²⁵⁻³⁴

DEFINITIONS

The terms chronic bronchitis, emphysema, and asthma have long been used diagnostically, but the criteria on which the respective diagnoses are based have only lately been clearly stated. This is particularly true for certificates of mortality or morbidity that form the basis for vital statistics. It has become apparent during the past 20 years that chronic bronchitis and emphysema have often been used as if they were synonymous. Furthermore, medical practice may result in the use of one term in one country and another in a second. This clearly is the case in the United States and the United Kingdom, where the diagnostic confusion was pointedly indicated by Fletcher and his colleagues³⁵ in a paper entitled "American Emphysema and British Bronchitis." An epidemiologist can do little to improve diagnoses already certified, though combining the statistics on chronic respiratory diseases may reduce error.³⁶ Much can and has been done, however, to make the future diagnosis of these diseases more precise, particularly in surveys designed to study them.

Ciba Conference Recommendations

The 1959 Ciba Conference on Terminology, Definitions, and Classification of Chronic Pulmonary Emphysema and Related Conditions³⁷ examined the general principles of definition of emphysema, and recommended that definition and classification of emphysema be based on morbid anatomical terms. Clinical definitions and classifications of the chronic respiratory diseases were also presented at the Conference. The recommendations of the Conference follow.

Emphysema - According to the Conference, "emphysema is a condition of the lung characterized by increase beyond the normal in the size of the air spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls."

Emphysema can be diagnosed and classified consistently only with preparations from lungs distended and fixed before they are cut. The simplest technique is intra-bronchial infusion of fixative. In some cases, identification of the anatomical origin of enlarged spaces may require such methods as the study of serial sections or stereoscopic microscopy of lung slices.

The Conference stressed the need to establish the normal range of air space sizes according to age and sex by each technique of lung preparation in order to establish the upper limits of normality. The two classifications suggested are outlined below.

- A. First classification.
 1. Nonselective distribution beyond the terminal bronchiole (panacinar emphysema).
 - a. Dilatation alone (for example, compensatory emphysema and emphysema resulting from partial obstruction of the main bronchus).
 - b. Destruction of the walls of the air spaces (panacinar destructive emphysema).
 2. Selective distribution beyond the terminal bronchiole.
 - a. Predominantly affects respiratory bronchioles.

- (1). Dilatation alone (for example, focal emphysema resulting from dust).
- (2). Destruction of walls of air spaces (centrilobular emphysema).
- b. Predominantly affects alveolar ducts and sacs.
 - (1). Dilatation alone.
 - (2). Destruction.
- 3. Irregular distribution beyond the terminal bronchiole (irregular emphysema).
- B. Second classification.
 - 1. Dilatation alone.
 - a. Nonselective distribution (compensatory emphysema and emphysema resulting from partial obstruction of the main bronchus).
 - b. Selective distribution predominantly affecting respiratory bronchioles (for example, focal emphysema resulting from dust).
 - 2. Destruction of walls of air spaces.
 - a. Nonselective distribution (panacinar destructive emphysema).
 - b. Selective distribution that predominantly affects respiratory bronchioles (centrilobular emphysema).
 - c. Irregular distribution (irregular emphysema).

Chronic nonspecific lung disease - The term "chronic nonspecific lung disease" was recommended by the Ciba Conference for the whole group of diseases variously referred to as "chronic bronchitis," "asthma," and "emphysema." The group as a whole was defined as comprising those diseases characterized by one or more of the following: chronic cough with expectoration, and paroxysmal or persistent excessive breathlessness, neither of which is solely attributable to:

- 1. Localized lung disease of any kind (for example, tuberculosis, pneumonia, or bronchiectasis cystic disease).
- 2. Generalized specific infective lung diseases (for example, miliary tuberculosis).
- 3. Pneumoconiosis.
- 4. Collagen diseases and the generalized pulmonary fibroses and granulomata.
- 5. Primary cardiovascular renal diseases.
- 6. Diseases of the chest wall.
- 7. Psychoneurosis.

Chronic nonspecific lung disease may coexist with any of the diseases referred to in 1 through 7 above. For instance, in a case of healed tuberculosis or of simple pneumoconiosis, the symptoms may be the result of chronic nonspecific lung disease. In such cases, two independent diagnoses should be made. Psychoneurosis is excluded only if there is no somatic effect; thus, psychogenic asthma is included if there is narrowing of the airways.

In an attempt to clarify the present confusion in the clinical use of the terms chronic bronchitis, asthma, and emphysema, the Ciba Conference proceeded to

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In an attempt to clarify the present confusion in the clinical use of the terms chronic bronchitis, asthma, and emphysema, the Ciba Conference proceeded to

define these components as given below.

Chronic bronchitis - Chronic bronchitis refers to the condition of subjects who have chronic or recurrent excessive mucous secretion in the bronchial tree. The diagnostic criterion, which is clinical, is chronic or recurrent cough with expectoration that is not attributable to conditions excluded from chronic nonspecific lung disease. Infection of the bronchi is frequently but not necessarily present.

The Conference went on to point out that, not infrequently, subjects who produce sputum deny cough. Such subjects are included as having bronchitis. Subjects who habitually swallow sputum should also be included as having chronic bronchitis. Opinion is divided concerning the significance of "dry" chronic bronchitis without hypersecretion, which is excluded by this definition. In Britain, however, population surveys suggest that persistent cough without expectoration is uncommon.

The words "chronic" or "recurrent" were defined as "occurring for most days for at least 3 months in the year during at least 2 years."

Generalized obstructive lung disease - Generalized obstructive lung disease refers to the condition of subjects who have widespread narrowing of the bronchial airways, at least on expiration, that causes abnormal resistance to airflow.

There may be no clinical symptoms or signs in the presence of demonstrable obstruction to bronchial airflow. Symptoms, when present, include paroxysmal or persistent breathlessness, tightness in the chest, and wheezing. The most characteristic sign is sibilant rhonchi, but their presence is not closely related to the severity of the obstruction.

1. Intermittent or reversible obstructive lung disease (asthma). Asthma refers to the condition of subjects having widespread narrowing of the bronchial airways that changes in severity over short periods of time, either spontaneously or as a result of treatment with bronchodilator drugs (including corticosteroids).
2. Irreversible or persistent obstructive lung disease. Irreversible or persistent obstructive lung disease refers to the condition of subjects having widespread narrowing of the bronchial airways that has been present for more than 1 year and that is unaffected by bronchodilator drugs (including steroids).

These definitions were adopted in 1961 by the World Health Organization (WHO) Committee on Cor Pulmonale.³⁸ With relatively minor alterations, they have been accepted by the European Coal and Steel Community.³⁹

American Thoracic Society Recommendations

The Committee on Diagnostic Standards for Non-Tuberculosis Respiratory Diseases of the American Thoracic Society suggested the definitions that follow.⁴⁰

Chronic bronchitis - Chronic bronchitis is a clinical disorder characterized by excessive mucous secretion in the bronchial tree. It is manifested by chronic or recurrent productive cough, which, according to this definition, should be present on most days for a minimum of 3 months in the year and for not less than 2 successive

years. The diagnosis can be made only after excluding other bronchpulmonary or cardiac disorders, which may cause identical symptoms, as the sole cause for the symptoms.

Asthma - Asthma is a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity spontaneously or as a result of therapy. The term "asthma" is not appropriate for the bronchial narrowing that results solely from widespread bronchial infection, such as acute or chronic bronchitis; from destructive diseases of the lung, such as pulmonary emphysema; or from cardiovascular disorders.

Emphysema - Pulmonary emphysema is an anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls. The Committee suggested the classification of emphysema given below.

1. Paracicatricial: Overdistension of air spaces and destruction of alveolar walls anatomically adjacent to fibrotic lesions of the lung.
2. Lobular: Overdistension of air spaces and destruction of of alveoli within the secondary lobule. The lesions can be subdivided on the basis of distribution and extent:
 - a. Centrilobular: Lesions are localized in relation to the respiratory bronchioles and predominate in the central part of the secondary lobule.
 - b. Panlobular: Lesions are distributed more or less uniformly throughout the secondary lobule.
 - c. Unclassified: Overdistension of air spaces with marked destruction of most of the secondary lobule. Because the intralobular changes are extensive, the original localization of lesions within the lobule cannot be defined.

To describe the extent of the lesions, a physician's report should indicate whether the disease is present in one or both lungs and should identify the specific segments involved.

The Committee's report describes the clinical and radiological manifestations of these diseases; indicates the main laboratory findings and physiological disturbances that may occur in each; and, finally, summarizes the pathological changes that may be observed.

Reid^{41,42} points out that "dilatation" and "destruction" as used in this definition imply a mechanism that is often not at work. She suggests, as a more suitable definition, the more factual statement that emphysema is a condition of the lung characterized by an increase beyond normal in the size of air spaces distal to the terminal bronchiolus, that is, the acinus.

The Committee on the Etiology of Chronic Bronchitis of the British Medical Research Council suggested⁴³ the following simple classification of chronic bronchitis on the basis of the Ciba Conference recommendations:

1. Simple chronic bronchitis. Chronic or recurrent increase in the volume of mucoid bronchial secretion sufficient to cause expectoration.
2. Mucopurulent chronic bronchitis. Chronic bronchitis in which the sputum is persistently or intermittently purulent and the sputum purulence is not the result of localized bronchopulmonary disease.
3. Chronic obstructive bronchitis. Chronic bronchitis with persistent widespread narrowing of the bronchial airways, at least on expiration, that causes increased resistance to airflow.⁴⁴

SCOPE OF PROBLEM

Between 30,000 and 40,000 people die in the United States each year from chronic respiratory diseases. An additional 50,000 to 60,000 deaths occur in which these diseases are mentioned as contributory causes. The number of deaths from emphysema and chronic bronchitis is doubling every 5 years: deaths from these causes increased from 12,426 in 1960 to 23,432 in 1965. About 15,000 middle-aged Americans are disabled each year by these diseases. Social Security Administration records indicate that nearly 10 percent of all disability awards granted from 1959 to 1962 were for chronic respiratory diseases (Table 1). Emphysema (51,508 awards from 1959 to 1962) is now second to coronary heart disease (131,160 awards in the same period) as the leading cause of Social Security-compensated disability.⁴⁵ The Social Security Administration is paying out \$90 million annually to support people disabled by chronic respiratory diseases. Furthermore, it is estimated that in addition to the toll taken by disablement 250 million man-hours are lost each year because of these diseases.

Table 1. DISABLING RESPIRATORY CONDITIONS AMONG MEN UNDER 65 YEARS OF AGE GRANTED DISABILITY AWARDS BY THE SOCIAL SECURITY ADMINISTRATION, 1959 to 1962⁴⁵

Condition	ISC ^a	Total	Age, years					
			35	35-44	45-49	50-54	55-59	60-64
Chronic bronchitis	502	2,846	58	222	308	518	770	970
Pneumoconiosis of occupational origin	523;524	9,538	14	206	598	1,834	3,202	3,684
Bronchiectasis	526	906	38	126	118	158	194	272
Emphysema	527	51,508	194	2,050	3,302	8,586	15,430	21,946
Total: Respiratory		64,798	304	2,604	4,326	11,096	19,596	26,872
Total: All causes		691,028	32,316	75,460	65,236	118,422	168,346	231,248

^aInternational Statistical Code.

In England and Wales, which have a total population one-fourth that of the United States, between 25,000 and 30,000 deaths have resulted from bronchitis each year for many years, the number depending to some extent on the annual prevalence

of influenza. Roughly 25 million working days are lost each year because of bronchitis⁴⁶ and about 10 percent of all contacts between patients and their general practitioners is for treatment of bronchitis. The annual cost to the country has been estimated at some 70 million pounds sterling (\$175 million).⁴⁷

In addition to the studies carried out in the United States and the United Kingdom, studies on chronic respiratory diseases have been conducted in many other countries, notably Belgium, The Netherlands, France, Germany, Czechoslovakia, Canada, and Australia.^{24, 39, 48-53}

Deaths from chronic respiratory diseases in the United States comprise about 2 percent of all deaths (Table 2). This is slightly less than the proportion of deaths attributed to cancer of the respiratory system, but about six times that now caused by respiratory tuberculosis. Chronic respiratory diseases are responsible for 5.8 percent of all deaths in England and Wales.

Table 2. DEATHS AND PERCENTAGE DISTRIBUTIONS OF RESPIRATORY DISEASE:
UNITED STATES AND UNITED KINGDOM, 1967

Cause of death	ISC	United States		United Kingdom	
		Number of deaths	Respiratory disease, % distribution	Number of deaths	Respiratory disease, % distribution
All causes		1,851,323	100.0	542,516	100.0
Chronic respiratory disease					
Asthma	241	4,137	0.2	1,757	0.3
Bronchitis (chronic, unqualified)	501; 502	5,306	0.3	25,887	4.7
Emphysema (no mention of bronchitis)	527.1	20,875	1.1	1,225	0.2
Pneumoconiosis	523; 524	1,640	0.1	566	0.1
Other chronic interstitial pneumonia	525	4,219	0.2	467	0.1
Bronchiectasis	526	1,476	0.1	1,177	0.2
Other	527.0; 527.2	2,790	0.2	279	0.1
Total		40,443	2.2	31,358	5.8
Cancer of trachea, bronchus, and lung	162; 163	54,407	2.9	28,252	5.2
Tuberculosis of respiratory system	001-008	6,351	0.3	1,798	0.3

Table 3 gives the number of deaths from chronic respiratory disease and the death rates by sex and color for the United States and, for comparison, the

Table 3. DEATHS AND DEATH RATES FOR DISEASES OF THE RESPIRATORY SYSTEM BY COLOR AND SEX:
UNITED STATES AND UNITED KINGDOM, 1967

Cause of death	ISC	United States						England and Wales			
		Number of deaths			Rate ^a			Number of deaths		Rate ^a	
		White		Nonwhite		White		Male	Female	Male	Female
		Male	Female	Male	Female	Male	Female				
Upper respiratory infection	470 through 475	238	194	82	78	0.3	0.2	59	62	0.3	0.2
Influenza	480 through 483	549	695	99	132	0.6	0.8	375	501	1.6	2.0
Pneumonia	490 through 493	25,895	20,620	5,361	3,541	30.4	23.2	14,443	17,683	62.6	72.2
Bronchitis	500 through 502	4,243	1,497	355	169	5.0	1.7	20,487	7,324	86.9	29.5
Acute	500	469	337	88	64	0.6	0.4	972	952	4.1	3.8
Unqualified	501	386	279	68	56	0.5	0.3	647	624	2.7	2.5
Chronic	502	3,388	881	199	49	4.0	1.0	18,868	5,748	80.1	23.2
Other diseases of respiratory system	510 through 527	24,874	6,279	2,036	788	29.2	7.1	3,254	1,641	13.8	6.6
Chronic interstitial pneumonia	525	2,368	1,201	378	272	2.8	1.4	306	161	1.3	0.6
Bronchiectasis	526	859	496	79	42	1.0	0.6	775	402	3.3	1.6
Other diseases of lung and pleura	527	18,698	3,520	1,174	273	22.0	4.0	1,134	370	4.8	1.5
Emphysema (no mention of bronchitis)	527.1	17,025	2,808	859	147	20.0	3.2	973	252	4.1	1.0
Cancer of trachea, bronchi, or lung	160 through 165	44,909	9,408	4,932	953	52.8	10.6	24,312	4,977	103.2	20.0
Respiratory tuberculosis	162; 163	40,959	8,217	4,424	807	48.2	9.3	23,548	4,704	99.9	18.9
Asthma	241	3,408	1,188	1,275	480	4.0	1.3	1,321	477	5.6	1.9
		1,909	1,490	377	361	2.2	1.7	779	978	3.3	3.9

^aDeaths/100,000.

corresponding figures for England and Wales. The higher rates for influenza, pneumonia, bronchitis, and respiratory cancer in England and Wales are striking, while the higher rates for "other diseases of the respiratory system" in the United States, particularly among the white population, are clear. The table also shows higher rates for chronic bronchitis and "other diseases of the respiratory system" in men than in women; higher rates for the white population than for the nonwhite; and higher rates for pneumonia than for any other respiratory disease in the nonwhite population.

These mortality statistics are based on the underlying cause of death. It is now generally recognized that chronic respiratory diseases may often be present at and contribute to death but still not be reflected in the vital statistics. Moriyama⁵⁴ concluded in 1963 that about 62 percent of all chronic respiratory disease present at death was certified as the underlying cause of death; however, Table 4, from the paper by Dorn and Moriyama,⁵⁵ suggests that this was an overestimate. It indicates that only about a third of all persons who die of chronic respiratory disease are certified as dying of it. Furthermore, chronic obstructive lung disease is often omitted as a contributory cause of death, with the result that the disease goes unreported.^{56, 57}

Chronic respiratory disease is a common cause of morbidity and disability. Data from the U.S. National Health Survey indicate that chronic respiratory disease comprises approximately 10 percent of all conditions that cause disability for 1 week or more. From July 1964 through June 1965, 1.9 percent of men and 2.0 percent of women aged 17 years and over who were interviewed in the U.S. National Health Survey reported that they had chronic bronchitis and/or emphysema.⁵⁸ Epidemiological studies have indicated that the prevalence in the national population of chronic respiratory disease of all degrees of severity varies from under 10 percent to over 40 percent, depending on age, sex, and the definitions of chronic respiratory disease that are used.

Table 4. DEATHS FOR WHICH SELECTED DISEASES WERE CODED AS UNDERLYING AND AS CONTRIBUTORY CAUSES OF DEATH: UNITED STATES, 1955^a

Diagnosis	ISC	Death certificates	Deaths for which diagnosis was selected as		Underlying cause, % of total
			Underlying cause	Contributory cause	
Asthma	241	13,047	5,904	7,143	45.3
Bronchitis, acute	500	2,179	1,067	1,112	49.0
Bronchitis, other	501; 502	5,876	2,025	3,851	34.5
Other chronic interstitial pneumonia	525	6,212	2,289	3,923	36.8
Bronchiectasis	526	5,363	2,197	3,166	41.0
Emphysema without mention of bronchitis	527.1	12,411	3,902	8,509	31.4
Other lung diseases	527.0; 527.2	16,814	2,129	14,685	12.7

^a Data from Dorn and Moriyama.⁵⁵

DISTRIBUTION OF CHRONIC RESPIRATORY DISEASE

TEMPORAL EFFECTS

Secular Trends

In the United States, death rates from chronic bronchitis, emphysema, and asthma declined steadily during the first half of the twentieth century. Since 1948, however, rates have risen steadily for deaths resulting from chronic respiratory disease.^{18, 54, 59, 60} The main rise has been in deaths from emphysema, but there have been smaller rises in death rates for bronchitis (in men) and also for "other chronic interstitial pneumonia" (Table 5). To what extent the trend in mortality for emphysema is real, and to what extent it reflects changes in diagnostic practice, is debatable. The rise is seen in men and women and in white and non-white persons. This might suggest that much of the rise is more apparent than real inasmuch as the marked predilection of males for the disease might be expected to result in a more rapid rise in them than in females. Supporting this interpretation is the similarity in the trends in all states and several cities.⁶² The increase is not the result of a shift in reporting chronic respiratory diseases from contributory to underlying cause of death, since the trend is seen for both categories.⁶³ This perhaps suggests that some of the trend in mortality reflects a real increase in incidence.

Katz and Kunofsky⁶⁴ have attributed the rise in emphysema mortality to tuberculosis. They found an association between tuberculosis and emphysema in death certificates in upstate New York in 1961, an association that was much less frequent before the availability of antimicrobial drugs for the treatment of tuberculosis. They also point out that a high frequency of emphysema was found by lung function tests in patients with tuberculosis.⁶⁵ They postulate that chemotherapy reduces the number of deaths from tuberculosis and that as a result the patients live long enough to develop emphysema secondary to the extensive destruction of lung tissue caused by tuberculosis. The evidence for this hypothesis is unconvincing. The high proportion of mortality from emphysema in tuberculous patients shown in their paper is associated with high proportional mortality from respiratory cancer. This might suggest that respiratory causes of death tend to be better certified in tuberculous patients than in other people. The authors do not indicate whether the age distribution of those dying from tuberculosis is the same as that of the general population. A difference in age could make a big difference in the proportional mortality rates. A more likely explanation would seem to be that the rise is attributable to the increase in cigarette consumption that occurred during the earlier decades of this century. This explanation has been questioned, however, by Barach and Segal.⁶⁶ They note that the increase in reported deaths from chronic bronchitis and emphysema have taken place during a period in which there is evidence⁶⁷ of a decline in cigarette smoking. Damage to the lungs from smoking, however, may take place many years before death. Consequently, one should not necessarily expect a close association between incidence of smoking and mortality.

A trend of increasing mortality from chronic respiratory disease has been noted in certain other countries. For example, in Canada, an increase in death rates for emphysema and chronic bronchitis has occurred that is somewhat similar, though less marked, to that seen in the United States.⁴⁸ Increases have also been noted in

Table 5. TRENDS IN MORTALITY FROM MAJOR CHRONIC RESPIRATORY DISEASES IN THE UNITED STATES,
1940 THROUGH 1967⁶¹

Year	Deaths/100,000-yr							
	Cancer of lung and bronchus	Tuberculosis (respiratory system)	Asthma	Chronic bronchitis ^a	Bronchiectasis	Other chronic inter- stitial pneumonia	Emphysema	Subtotal ^b
1940	4.2	42.2	1.7	2.1	-- ^d	-- ^d	0.1	-- ^c
1941	4.6	40.8	1.8	1.9	--	--	0.1	--
1942	4.8	39.6	1.7	1.9	--	--	0.1	--
1943	5.4	39.0	2.0	2.0	--	--	0.1	--
1944	5.8	38.2	2.0	1.9	--	--	0.2	--
1945	6.2	36.9	1.9	1.8	--	--	0.2	--
1946	6.4	33.5	1.8	1.7	--	--	0.2	--
1947	6.8	31.0	1.9	1.8	--	--	0.2	--
1948	7.3	27.7	1.8	1.8	--	--	0.3	--
1949	11.2	24.2	3.1	1.5	1.5	0.6	0.6	1.5
1950	12.2	20.6	2.9	1.3	1.4	0.7	0.8	1.4
1951	12.9	18.5	4.5	1.3	1.4	0.8	1.1	1.4
1952	13.8	14.4	4.5	1.2	1.4	1.0	1.2	1.4
1953	14.9	11.3	4.3	1.3	1.5	1.2	1.6	1.5
1954	15.4	9.3	3.8	1.2	1.3	1.2	1.9	9.4
1955	16.3	8.3	3.6	1.2	1.3	1.4	2.2	9.7
1956	17.5	7.8	3.6	1.2	1.3	1.6	2.7	10.4
1957	18.1	7.3	3.9	1.4	1.3	1.8	3.4	11.8
1958	18.6	6.6	2.9	1.5	1.4	2.0	3.9	11.7
1959	19.4	6.0	2.8	1.5	1.3	2.0	4.4	12.0
1960	20.3	5.6	3.0	1.8	1.3	2.2	5.2	13.5
1961	21.2	5.0	2.7	1.6	1.2	2.1	5.6	13.2
								39.4

Table 5 (continued). TRENDS IN MORTALITY FROM MAJOR CHRONIC RESPIRATORY DISEASES IN THE UNITED STATES,
1940 THROUGH 1967⁶¹

Year	Deaths/100,000-yr						
	Cancer of lung and bronchus	Tuberculosis (respiratory system)	Asthma	Chronic bronchitis ^a	Bronchiectasis	Other chronic inter- stitial pneumonia	Emphysema
1962	22.3	4.7	2.6	1.9	1.1	2.2	6.7
1963	23.1	4.6	2.7	2.3	1.1	2.3	8.0
1964	23.9	4.0	2.3	2.3	1.0	2.2	8.3
1965	25.0	3.8	2.3	2.5	0.9	2.2	9.6
1966	26.3	3.6	2.2	2.7	0.8	2.2	10.3
1967	27.5	3.2	2.1	2.7	0.7	2.1	10.6
							Subtotal ^b
							41.5
							44.1
							44.0
							46.3
							48.1
							48.9

^aIncludes unspecified chronic bronchitis.

^b"Asthma" through "emphysema" columns.

^cData not comparable.

^dData not available.

The Netherlands, in Israel,⁶⁸ and in the United Arab Republic.⁶⁹

In England and Wales, mortality rates for bronchitis declined steeply from about 1850 to 1940.²⁶ The rates, which were always higher in men, declined somewhat less rapidly in men than in women. Since 1940, mortality rates in women have shown a continuing decline, though the decline is slower than before 1940; but in men, a modest increase in mortality rates has occurred since 1940. There is little indication that the mortality rates have been affected by the introduction of antibiotic drugs. Chronic bronchitis is therefore in marked contrast to respiratory tuberculosis in this respect. In Scotland, the death rates from bronchitis from 1940 to 1960 were about 25 percent lower than in England and Wales.⁷⁰ During this period, the rates declined in women, but showed an increase in men, especially from the early 1950's.

The major long-term trend in chronic respiratory disease mortality noted in recent years in the United Kingdom is an increase in mortality rates for asthma.^{71, 72} The increase has affected mainly the 5- to 34-year age group and is most pronounced at ages 10 to 14 years. In this last age group, mortality rates increased nearly eightfold in 7 years, and, in 1966, asthma accounted for 7 percent of all deaths. Smaller increases have been noted in other countries; increases at ages 10 to 19 have been observed in Australia, Japan, Western Europe, and the United States.⁷³⁻⁷⁵ In Britain, general practitioners' records provide no evidence for an increase in prevalence; it therefore seems likely that there has also been an increase in case fatality. No environmental hazards are known that could have increased the severity of the disease. Thus, new methods of treatment, notably with pressurized aerosols of sympathomimetic drugs, are believed to be responsible for the observed increase in mortality rates.^{76, 77}

Seasonal Variations

Marked seasonal variations occur in mortality and morbidity from chronic respiratory diseases through the year. Mortality for bronchitis in the United Kingdom is much higher in the winter than in the summer. Marked seasonal variations in respiratory disease morbidity were also noted in the United States, according to the U.S. National Health Survey.

SPATIAL EFFECTS

International Differences

Despite the obvious limitations of differences in diagnosis, certification, and coding, mortality statistics have pointed to differences in chronic respiratory disease frequency between countries; such differences have stimulated productive research.^{47, 78-83} In earlier years, comparative rates for bronchitis were given annually by the World Health Organization (Table 6).⁸⁴ Statistics of this kind, based on a single disease rubric, are particularly likely to exaggerate differences between two countries when one of the countries classifies most of the respiratory disease deaths under a different rubric. Comparisons are likely to be more valid if all the chronic respiratory disease rubrics are considered, as is the present practice of the World Health Organization. The fortyfold difference in bronchitis mortality between the United Kingdom and the United States is reduced to a more reasonable one of threefold to fourfold when all chronic respiratory diseases are combined (Table 7). The World Health Organization now gives mortality rates for bronchitis and other diseases of the respiratory system separately (excluding acute infections and upper respiratory conditions) (Table 8).⁸⁵

Table 6. BRONCHITIS MORTALITY RATES BY SEX FOR SELECTED COUNTRIES, 1962^a
(deaths/100,000)

Country	Male	Female
England and Wales	103.1	41.4
Czechoslovakia	54.4	26.0
Italy	38.7	25.3
New Zealand	35.9	10.5
Australia	28.6	6.1
Belgium	25.0	9.4
Denmark	22.4	9.7
Japan	9.5	8.3
Sweden	5.1	4.1
United States	3.6	1.4
Israel	3.4	1.3

^aData from WHO Annual Epidemiological and Vital Statistics.⁸⁴

Table 7. MORTALITY RATES FOR DISEASES OF THE RESPIRATORY SYSTEM IN THE
UNITED STATES, ENGLAND, AND WALES, 1962⁸⁵
(deaths/100,000)

Disease	ISC	Males		Females	
		United Kingdom	United States (white)	United Kingdom	United States (white)
All respiratory		189.5	60.2	124.4	34.0
Acute upper	470 through 475	0.3	0.4	0.2	0.3
Influenza	480 through 483	6.7	1.7	7.5	1.8
Pneumonia	490 through 493	66.0	32.4	69.7	24.6
Bronchitis	500 through 502	103.1	3.7	41.4	1.4
Other	510 through 527	15.6	22.0	6.8	5.9

Intranational Differences

Mortality rates for chronic respiratory diseases differ between parts of the United States. Certain states have exceptionally high rates: Arizona, Wyoming, New Hampshire, Vermont, and Florida, among others. Differences in age distribution of the population of different states can explain some of the high rates. Climate, air pollution, occupational exposures, and density of population may also be contributing factors. In addition, immigration of persons with respiratory disease into some of these states and climates also presumably plays a role in the high rates.

Table 8. MORTALITY RATES FOR BRONCHITIS AND OTHER CHRONIC RESPIRATORY DISEASES BY SEX FOR SELECTED COUNTRIES, 1967^a
(deaths/100,000)

Country	Bronchitis, chronic and unqualified		Other chronic respiratory diseases ^b	
	Male	Female	Male	Female
England and Wales	83.2	25.7	13.3	6.2
Italy	39.1	20.3	11.4	4.8
Australia	34.2	6.2	8.9	4.1
Belgium	25.3	7.2	50.9	17.4
Germany (Fed. Rep.)	24.4	8.5	19.9	5.9
Denmark	22.7	8.9	10.5	4.1
Netherlands	18.2	5.7	18.2	6.1
Canada	10.0	2.1	13.8	4.3
Norway	7.3	3.0	6.3	2.6
United States	4.2	1.3	27.0	6.7
Japan	3.4	2.7	4.1	2.1

^aData from WHO Annual Epidemiological and Vital Statistics.⁸⁵

^bRespiratory diseases other than bronchitis and acute infections and upper respiratory conditions.

In Canada, Anderson has drawn attention to the large differences that exist in the mortality rates for different chronic respiratory diseases in different provinces. Much of this variation is explained by diagnostic practice and the degree to which lung function tests are used in different places. When diagnostic categories are combined, however, considerable variation still exists.⁸⁶

In the United Kingdom, mortality rates are high in the northeast, northwest, and in South Wales; and low in East Anglia. Climate, weather, density of population, industrial concentration, and pollution are some of the factors that are thought to contribute to these differences.

Urban-Rural Differences

In England and Wales, a close association exists between bronchitis death rates and density of population. For both men and women, regardless of age group, the rates are approximately twice as high in cities with 100,000 inhabitants and over as in rural areas. One interesting change that has taken place during the past 10 years is that hardly any difference now exists between the bronchitis death rates of conurbations and of other cities with 100,000 inhabitants or more. For men, but not for women, differences between urban and rural mortality rates for chronic respiratory disease are smaller in the United States than in the United Kingdom.^{83,87}

SOCIOECONOMIC EFFECTS

In England and Wales, mortality rates have for many years been roughly six times greater in the lower socioeconomic strata than in the higher.^{44,88,90} In

the United States, also, a twofold difference exists in mortality rates for chronic respiratory disease, among employed males, between the professional class and those in unskilled jobs (Table 9). More recently, in Britain, a similar socioeconomic gradient was shown to exist for morbidity.⁹¹ The possibility that differences in the standards of medical care received by different segments of the population might explain the observed mortality gradient is unlikely in view of the improvements that followed the introduction of the National Health Service in Britain in 1948. Differences in the quality of care do not seem likely to account for the differences in morbidity among social classes. Occupational factors, particularly differences in exposure to respiratory irritants, will be discussed at length later. Other explanations that have been offered are housing conditions, with domestic overcrowding among the poor and, consequently, greater opportunity for cross-infection; the too early return to work after a respiratory infection;⁸⁸ the situation of the poor in the more polluted areas of cities; and social drifts whereby those with chronic respiratory disease tend to decline in socioeconomic standing.⁹²

Table 9. MORTALITY RATIOS BY OCCUPATION FOR MEN AGED 20 THROUGH 64 IN THE UNITED STATES, 1950

Occupational level	Standardized mortality ratios	
	Diseases of respiratory system ^a	Asthma
All occupations	100	100
Professional workers	72	71
Technical, administrative, and managerial workers ^b	52	79
Clerical, sales, and skilled workers	87	104
Semiskilled workers	149	99
Laborers ^b	157	145
Agricultural workers	75	95

^aInfluenza and pneumonia excluded.

^bFarm workers excluded.

METHODOLOGY FOR EPIDEMIOLOGICAL STUDIES OF CHRONIC RESPIRATORY DISEASE

DIAGNOSIS AND INVESTIGATION

Standardized Questionnaires

It was noted early in epidemiological studies of chronic bronchitis that clinical examination of the chest added little useful information.⁹³ Therefore this procedure has been omitted in most surveys and reliance has been placed, instead, on answers to questions about respiratory symptoms. In order to obviate the variation that can occur when different observers question people about their respiratory symptoms,⁹⁴ a great deal of effort has been devoted to the formulation of precise questions,⁹⁵⁻⁹⁸ culminating in the publication by the British Medical Research Council's Committee on Chronic Bronchitis of recommended questionnaires for recording respiratory symptoms, together with instructions for their use.^{43, 99} These questionnaires have been widely distributed, translated into many languages, and used for respiratory surveys in many different countries.¹⁰⁰⁻¹⁰³ Though there are still problems with reproducibility,^{104, 105} the questionnaires have led to a considerable degree of standardization of the results of different research workers and to improved comparability of results.

Self-administered Questionnaires

Most questionnaires have been completed by physicians or health visitors in a personal interview. Some attempts have been made to use information collected by means of self-administered questionnaires. Fletcher and Tinker¹⁰⁶ noted in a survey that answers on cough, phlegm, dyspnea, and smoking habits on a self-administered questionnaire disagreed somewhat from answers on an interviewer-administered questionnaire. The self-administered questionnaire was not returned, or was incompletely filled in, however, by about 25 percent of the men under study. This error rate was only 7 percent in a group of post office clerks and Fletcher and Tinker concluded that the self-administered questionnaire might be especially useful in persons accustomed to clerical work. Fletcher and his colleagues¹⁰⁷ used a self-administered questionnaire to detect men with persistent cough and sputum in the first stage of their study of men engaged in clerical and light engineering work in West London. McNab and his colleagues¹⁰⁸ successfully surveyed men aged 55 to 64, living in several areas in East Anglia, by means of a self-administered questionnaire. Of the households selected, 86 percent responded; this response was increased to 98 percent by home visitation. In the United States, Sharp and his colleagues¹⁰⁹ obtained good agreement between self-administered and interviewer-administered questionnaires on respiratory symptom prevalence in an industrial population of nearly 2000 men in Chicago. Interviewer- and self-administered questionnaires have been used successfully by Higgins and his colleagues¹¹⁰ in Tecumseh, Michigan, but self-administered questionnaires were not satisfactory in a survey carried out by Higgins and his colleagues¹¹¹ in Marion County, West Virginia. Self-administered questionnaires were used successfully by Reid and his colleagues¹¹² in their study of migrants and, more recently, by Lambert and Reid¹¹³ in a large random sampling of the population of Britain. Self-administered questionnaires have also been used by Cederlof and his colleagues¹¹⁴⁻¹¹⁷ to record respiratory symptoms in towns in Sweden.

Cough and Sputum Tests

It is a well-known clinical observation that patients often say they have no cough but at the same time present clear evidence to the contrary. A few research workers, however, have made use of cough as an objective test. Thus, Greene and Bercowitz¹¹⁸ used a preoperative test cough "of proved sensitivity and reliability" to measure the prevalence of smokers' bronchitis in persons undergoing surgical operations. More recently, Gandevia has also advocated the use of a test cough in epidemiological studies of chronic respiratory disease.¹¹⁹⁻¹²¹ The procedure is as follows: the subject is asked to take a big breath, cover his mouth, and cough hard. The sign is recorded as positive if he produces any sputum; the cough sounds loose, or as if it could be productive on further effort; or the cough sounds as though it was productive but the sputum is swallowed.¹²²

Collection and measurement of the sputum brought up during the first hour after rising has been advocated by Elmes and his colleagues,¹²³ who showed that the volume of sputum correlated well with the FEV but that the degree of purulence and presence of pathogenic organisms did not. These observations were subsequently confirmed by Fletcher and Tinker.¹⁰⁶ Simple methods for examining the cellular content of sputum have been described by Miller,¹²⁴ who suggested a scheme for the visual grading of purulence in relation to the cell count. He stressed the importance of microscopic examination as an aid to differentiating purulent from purulent-looking sputum that contains only epithelial debris. Subsequently, Ashcroft¹²⁵ studied day-to-day variations in sputum volume in patients with chronic bronchitis, and Miller and his colleagues¹²⁶ made similar studies of working men. Variation from day to day was found to be considerable. Miller and his colleagues suggested that it is better to collect sputum over several days. Collection of sputum, measurement of its volume, and categorization of its nature have been included in surveys by a number of workers. Sputum has seldom been studied microscopically, however. The importance of detecting sputum eosinophilia in chronic bronchitis has been stressed strongly by Mulder,¹²⁷ but the observation of eosinophils has been of rather questionable value in epidemiological surveys. Possibly the greatest value of identifying sputum eosinophilia is in detecting cases of unsuspected asthma. It also provides some measure of allergy, which has often been claimed to be a factor in chronic bronchitis. Chodosh¹²⁸ has recently emphasized the importance of examining sputum to determine its detailed cytology. He has described examination techniques, types of cell found and their distribution in common respiratory syndromes, and interpretation of the findings. Although epidemiologists have certainly neglected this simple and useful procedure, it is clear that in future surveys a greater effort should be made to include sputum cytology.

Bacteriological examination of the sputum has not proved of much value in epidemiological surveys, although it is, of course, essential in assessing the role of infection and in controlling treatment. Bacteriological examination is considered at greater length in a separate section.

Lung Function Tests

Simple lung function tests have been used in most surveys. Measurements of the forced expiratory volume (FEV) and of the forced vital capacity (FVC) have been most widely used.^{129,130} Currently, the 1-second volume is almost universally employed. In earlier surveys, however, the 0.75-second volume was often used. It has been generally agreed that the actual value measured, rather than

some percentage of an expected normal value, should always be recorded and analyzed. (Formulae for prediction of normal values have been given by several groups of workers.¹³¹⁻¹³³) Other indices of ventilatory lung function that have been used in epidemiological studies include maximal expiratory flow rate (MEFR), maximal mid-expiratory flow rate (MMEF),¹³⁴ and maximal voluntary ventilation (MVV). In general, these measures correlate highly with the FEV. They have not been shown convincingly to be better than the FEV for field survey work.

Peak expiratory flow rates (PFR) have been measured in a considerable number of surveys. The popularity of this measure of ventilatory capacity resulted from the production of the simple and portable Wright peak flow meter.¹³⁵

Certain epidemiological studies have included additional tests of lung function. Nitrogen mixing has been used in a few studies.⁸¹ Airways resistance, using a Clements interruptor, was measured in an early survey in the Rhondda Fach (Medical Research Council unpublished data). More recently, airways resistance has been studied by means of the body plethysmograph, especially in relation to the effects of exposure to cotton dust and tobacco smoking.¹³⁶ A number of more sophisticated tests of lung function have been used by Ferris and his colleagues¹³⁷ in epidemiological surveys of respiratory disease. These include plots of volume versus flow, measurement of carbon monoxide diffusing capacity or transfer factor, and measurement of airways resistance by methods other than plethysmography.

Chest Radiographs

The radiographic signs of emphysema have been described by Kerley and his colleagues;¹³⁸ Parkinson and Hoyle;¹³⁹ Lodge;¹⁴⁰ and Simon and Galbraith.¹⁴¹ The latter summarized the characteristic radiographic features as a low, flat diaphragm; narrow vertical heart; abnormal vascular pattern; and bullous changes. These signs were essentially those used more recently by Simon (1964) (Table 10).¹⁴²

Table 10. RADIOGRAPHIC CRITERIA FOR DIAGNOSIS OF EMPHYSEMA^a

Radiographic category	Radiographic criteria
I. Excess air in the lungs	Low, flat diaphragm Large retrosternal space Poor diaphragmatic excursion
II. Cardiovascular changes	Narrow, vertical heart Prominent pulmonary trunk, even in the absence of right ventricular hypertrophy Large hilar with small lung vessels
III. Bullae	Avascular transradiant area With or without definite demarcation

^aAdopted from Simon.¹⁴²

Correlations between these abnormalities and diagnoses of emphysema based on clinical and physiological criteria, attempted by Whitfield et al.,¹⁴³ were not good. Knott and Christie¹⁴⁴ concluded that a single postero-anterior film was of doubtful significance, and that even with a complete set of films 10 percent of emphysema cases would be missed and a few normal individuals would be wrongly diagnosed as having emphysema. The limitations of the chest radiograph in the diagnosis of emphysema have also been noted by Reid and Millard¹⁴⁵ and by Simon and Reid.¹⁴⁶ Better results have been obtained when radiographic changes have been correlated with pathological changes found at autopsy.¹⁴⁷⁻¹⁴⁹ Few surveys of respiratory diseases have included lateral chest x-rays as well as a postero-anterior film. The findings from these studies indicate that lateral films should in the future be included in surveys of chronic obstructive lung disease. An additional advantage of using lateral as well as postero-anterior films is that lung volumes can be obtained, inasmuch as lung volumes measured radiographically have been shown to correlate highly with those measured by body plethysmography.¹⁵⁰

Morphological Changes

The morphological changes found in chronic bronchitis have been described by Reid.^{42,151,152} The essential characteristic is an increase in the mucous-secreting cells. Reid introduced simple measures for diagnosing and categorizing the severity of the disease, the most useful and most widely adopted of which has been the determination of the ratio of the thickness of the mucous gland layer to the thickness of the bronchial or bronchiolar wall--the gland/wall ratio.¹⁵³ According to Reid, the normal gland/wall ratio averages 0.26, with a range of 0.14 to 0.36; in patients with chronic bronchitis, the average is 0.59, with a range of 0.41 to 0.79. An increase in the number of goblet cells occurs *pari passu* with the increase in glandular layer, and may be especially numerous in bronchioli where normally they are sparse. The relationship of the gland/wall ratio to sputum production, smoking, chronic bronchitis, and emphysema is the subject of a number of studies.¹⁵³⁻¹⁵⁸

The extent, severity, type, and distribution of emphysema have been studied by many pathologists during the past 20 years^{157,159-164} and methods for assessing the changes in the lungs have been developed within the past 15 years.¹⁶⁵⁻¹⁷⁴ The diagnostic value of inflated lung sections, stressed by Gough et al. in 1952,¹⁷⁵ has been confirmed by subsequent studies.^{173,176-179} Interpretations of the presence or absence of emphysema and its type, extent, and severity have been shown to vary widely among different pathologists,¹⁸⁰ and measures for reducing these variations have been suggested.¹⁸¹ As an additional diagnostic aid, correlations between the morphological changes of emphysema and the preexisting clinical or physiological state have been made by many investigators.^{160,179,180,182-184}

Studies of the mechanisms of production of hypersecretion (such as by Reid¹⁸⁵) and of emphysema (such as by Gross and his colleagues¹⁸⁶) have been reviewed by Reid⁴² and by Wright and Kleinerman.¹⁸⁷

Measurement Reproducibility

The reproducibility of diagnostic measures of respiratory disease has been studied by a number of workers.^{95,96,98,105,106} The findings of Holland and his colleagues¹⁰⁵ may be considered to be representative. These workers concluded

that the answers to questions about respiratory symptoms in two standardized questionnaires were reasonably reproducible. The questionnaires also discriminated fairly well among persons categorized on the basis of more objective measurements such as the FEV or 1-hour sputum volume. The importance, however, of the precise wording of individual questions and the careful design of the questionnaire was noted. The study also demonstrated fairly good reproducibility of measurements of sputum volume and quality after an interval of 6 months.

STUDY POPULATIONS

The importance of the population used in studies of the epidemiology of respiratory disease has been discussed by Higgins.¹⁸⁸ The problems of drawing conclusions from hospital and clinic populations have been particularly stressed. Surveys of occupational groups have many points in their favor, and have been recommended by Reid.¹⁵³ Such groups, which have been studied often, are usually readily accessible, relatively stable, and generally somewhat uniform in socioeconomic background. They are particularly useful for international comparisons when the occupation is similar in different countries.^{80,189} Occupational groups do, however, have the disadvantage that considerable selection, which may be impossible to evaluate, may occur. Representative samples of the whole community are clearly preferable, although problems in defining and maintaining such groups may be great. The liability of all study groups to selection either by death or by migration has also been increasingly realized.

The vast majority of publications of surveys to date have been based on cross-sectional studies. More longitudinal data are needed so that some of the potential selection that has been suspected can be studied. A few longitudinal studies are now being carried out, from which some publications have already resulted.^{110,190-194} The main population studies conducted in the United States^{62,109,111,195-212} and in Britain and other European countries^{24,36,52,80,81,96,98,106,113,189,191,210,213-234} are summarized in Tables 11, 12, and 13. In addition to these, studies have been carried out in South Africa,^{235,236} Australia,²³⁷ India,^{162,238} and Japan.²³⁹

Table 11. AMERICAN FIELD STUDIES OF THE PREVALENCE OF BRONCHITIS

Authors/yr	Refer- ence	Area	Population	Sample, type and % of population	Number surveyed	Age range, yr	Methods
Pemberton, 1956	195	Pennsylvania	Mining, industrial, rural	Volunteers	611	45 to 64	Questionnaire
Bower, 1961	196	Denver, Colorado	Bank employees (urban)	Volunteers, 77 to 80%	95 men 77 women	40 to 70	Questionnaire, MMEF
Schoettlin, 1962	197	Los Angeles, California	Veterans' Adminis- tration domicili- ary and chronic disease hospital	100%	2622	Elderly males	Questionnaire, puffmeter
Brinkman and Coates, 1962	198	Detroit, Michigan	Industrial and other	Selected	1317 men (includes men with siliicosis)	40 to 65	Interview, VC, FEV _{1.0} , FEV _{3.0} , MMEF, chest x-ray
Ferris and Anderson, 1962	199	Berlin, New Hampshire	Industrial	Random, 95.9%	565 men 654 women	25 to 74	Questionnaire (MRC ^a), VC, FEV _{1.0} , PFR
Balchum <u>et al.</u> , 1962	200	Vernon, California	Urban employees	4505 chest x-rays	1456 men	10 to <60	Questionnaire, VC, FEV _{1.0} , FEV _{3.0} , peak flow
Goldsmith <u>et al.</u> , 1962	201	San Francisco, California	Longshoremen (urban)	Volunteers, 58%	3311 men	20 to >80	Interview, VC, FEV _{1.0} , puff- meter, chest x-ray
Gocke and Duffy, 1962	202	Jersey City, New Jersey	Housing units (urban)	90%	435 men	40 to 59	Questionnaire (MRC), FEV _{1.0} , chest x-ray
Prindle <u>et al.</u> , 1963	203	Seward and New Florence, Pennsylvania	Rural	100%	948 men and women	≤30	Questionnaire, lung function tests
Speizer and Ferris, 1963	204	Boston, Massachusetts	Road tunnel em- ployees (urban)	97%	60 men	25 to 74	Questionnaire, VC, PFR, FEV _{1.0}
Hyatt <u>et al.</u> , 1964	205	Raleigh County, West Virginia	Mining	Union members	267 men	45 to 58	Questionnaire, lung function tests

Table 11 (continued). AMERICAN FIELD STUDIES OF THE PREVALENCE OF BRONCHITIS

Authors/yr	Refer- ence	Area	Population	Sample, type and % of population	Number surveyed	Age range, yr	Methods
Payne and Kjelsberg, 1964	206	Tecumseh, Michigan	Urban	Random, 87 to 89%	2383 men 2607 women	16 to 79	Questionnaire, FEV _{1.0} , VC
Coates et al., 1965	207	Detroit, Michigan	Postal workers (urban)	79%	1584 men and women	≥40	Questionnaire (MRC), VC, FEV _{1.0} , sputum volume
Deane et al., 1965	208	San Francisco and Los Angeles, California	Outside telephone workers	76 to 83%	508 men	>40	Questionnaire (MRC), VC, FEV _{1.0} , puff- meter
Densen et al., 1965	62	New York City	Postal and transport workers	87%	5311 men	35 to 60	Questionnaire (MRC), FEV _{1.0} , absence records
Wynder et al., 1965	209	New York City, Los Angeles and Northern California	Patients and Seventh-Day Adventists	Selected	980 men	<30 to >70	Smoking and symptomatic inquiry
Holland and Stone, 1965	210	Eastern U.S.	Telephone workers	96.9%	625 men	>40	Questionnaire (MRC), VC, FEV _{1.0} , sputum volume
Sharp et al., 1965	109	Chicago, Illinois	Industrial workers (Western Electric)	Random	1887 men	43 to 58	Questionnaire (MRC), VC, FEV _{1.0} , MEFR, sputum volume
Anderson et al., 1965	211	Chilliwack, Brit- ish Columbia	Rural	Random, 95%	711 men and women	25 to 74	Harvard ques- tionnaire, VC, FEV _{1.0} , PFR
Enterline and Lainhart, 1967	212	Mullins and Rich- wood, West Virginia	Mining and other	Matched samples miners and nonminers	898	21 to 64	Questionnaire, FEV
Higgins et al., 1968	111	Marion County, West Virginia	Rural mining	83%	1106 men	20 to 69	Questionnaire, FVC, FEV _{1.0}

^aBritish Medical Research Council questionnaire.

Table 12. BRITISH AND COMPARATIVE FIELD STUDIES OF THE PREVALENCE OF CHRONIC BRONCHITIS

Author and year	Reference	Area	Population	Sample, type and % of population	Number surveyed	Age range, years	Methods ^a
Newell and Browne, 1955	213	County Durham	Miners	All men in 4 collieries, 89%	5,723	15 to 65	Questionnaire, chest x-ray
Higgins et al., 1956	214	Leigh (urban)	Miners and nonminers	Random, 90%	245	55 to 64	Questionnaire, FEV _{0.75} , chest x-ray
Higgins, 1957	215	Vale of Glamorgan (rural)	Men and women	Random, 91%	631	25 to 74	Questionnaire, FEV _{0.75} , peak flow rate, chest x-ray
Clifton, 1957	216	Sheffield (urban)	Men and women	Volunteers, 91.7%	2,519	15 to >60	Questionnaire, MBC, chest x-ray
Clifton, 1957	216	Wensleydale (rural)	Men	Volunteers, 97%	570	≥30	Questionnaire
Higgins and Cochrane, 1958	217	Annandale (rural)	Men and women	Random, 91%	206	55 to 64	Questionnaire, FEV _{0.75} , chest x-ray
Higgins et al., 1959	98	Staveley (urban)	Miners, foundry workers and other men	Random, 95%	776	25 to 34	Questionnaire, FEV _{0.75} , chest x-ray
Fletcher et al., 1959	96	London	Wives of men aged 55 to 64		334	55 to 64	Interview
Fletcher and Tinker, 1961	106	London	Post office men and women	Random	384	40 to 59	Questionnaire, FEV _{1.0} , sputum volume
College of General Practitioners, 1961	218	Rural and urban	London transport men	Random, 91%	513	30 to 59	Questionnaire, peak flow rate, sputum volume
Holland and Reid, 1965	219	London	Men and women	Random, 94%	1,630	40 to 64	Questionnaire, peak flow rate
		Gloucester, Norwich, Peterborough	Mail van drivers, maintenance men	London, 93.7%	477	40 to 59	MRC short questionnaire, peak flow rates
			Mail van drivers, engineering workers	Country towns, 94.6%	293		McKessen vitalor, FEV _{1.0} , peak flow rates

Table 12 (continued). BRITISH AND COMPARATIVE FIELD STUDIES OF THE PREVALENCE OF CHRONIC BRONCHITIS

Author and year	Reference	Area	Population	Sample, type and % of population	Number surveyed	Age range, years	Method ^a
Meadows <i>et al.</i> , 1965	220	London	Senior industrial staff (men)	Random, 97%	224	30 to 69	Questionnaire
Higgins <i>et al.</i> , 1968	191	Staveley (urban)	Miners, foundry and other men	Random, 90%	1,400	25 to 74	Questionnaire, sputum volume, FEV _{1.0} , FEV _{0.75}
Holland <i>et al.</i> , 1969	221	4 areas of Kent	School children	94% of those residing and attending school in the area	10,971	5 to 16	Questionnaire completed by parents: PFR
Ashford <i>et al.</i> , 1970	222	United Kingdom	Miners	Men in 25 collieries, 100%	29,984	15 to 65	NCB questionnaire, FEV, FVC
Colley and Reid, 1970	223	England and Wales	Primary school children in contrasting urban and rural areas	97.8%	11,135	6 to 10	Questionnaire to parents, examination by school medical officers
Lambert and Reid, 1970	113	England, Wales and Scotland	Representative sample of men and women	74% of those approached and able to respond in age group 35 to 69	9,975	35 to 69	Mailed self-administered questionnaire
Olsen and Gilson, 1960	81	Bornholm, Denmark	Comparative Small town (Rønne)	Studies Random, 91.5%	183	55 to 64	Questionnaire, FEV _{0.75} , PFR, chest x-ray
Mork, 1962	80	Bergen, Norway London	Transport workers Post office transport workers	98.4% 96.8%	189 150	40 to 59	Questionnaire, PFR, sputum volume
Reid <i>et al.</i> , 1964	36	England and Wales	Random samples	Selected from original samples	1,258	45 to 64	Questionnaire, PFR

Table 12 (continued). BRITISH AND COMPARATIVE FIELD STUDIES OF THE PREVALENCE OF CHRONIC BRONCHITIS

Author and year	Reference	Area	Population	Sample type and % of population	Number surveyed	Age range, years	Method ^a
Reid et al., 1964 (continued)	189	Berlin, New Hampshire			546	45 to 64	
Holland et al., 1965	210	London and small towns U.S. East Coast; Washington; Baltimore; Westchester, N.Y.	Post office van drivers Outside telephone workers	96.8 to 98% of available men	736 708	40 to 59 40 to 59	Questionnaire (MRC), FEV ₁ .0, sputum volume

^aQuestionnaires used in these surveys were either the original Medical Research Council (MRC) form or were modeled on it.

Table 13. EUROPEAN STUDIES OF THE PREVALENCE OF CHRONIC OBSTRUCTIVE LUNG DISEASES

Author and year	Reference	Area	Population	Sample, type and % of population	Number surveyed	Age range, years	Methods
Finland Huhti, 1965 Poppius <i>et al.</i> , 1965	224 225	Harjavalta 47 sites, E. Finland; controls, adjacent area	Rural Rural	Total Random sample	761 men, 925 women 975 forest workers 329 controls	40 to 64 20 to 59	Questionnaire, FEV ₁ , FVC MRC questionnaire, peak expiratory flow
France Kourilsky <i>et al.</i> , 1966 Freour <i>et al.</i> , 1966	52 226	Paris Bordeaux	Industrial Urban	Sample Representative sample	4992 men 484 women Men	30 to 60 30 to 70	Questionnaire, FEV ₁ , FVC Symptoms, lung function
Sweden Tibblin <i>et al.</i> , 1965 Julin and Wilhelmsen, 1964-1965	227 228	Goteborg Goteborg	Urban Urban	Random sample Stratified Random sample, 92.2%	339 men 1054 men 1113 women	50 16 to 64	MRC questionnaire MRC questionnaire, physical exam, Wright peak flow rate
Czechoslovakia Staneek <i>et al.</i> , 1966	229	Prague	Urban	Random sample; 1:6 men, (93.7%) 92% of one town district	473 men	60 to 64	Questionnaires (MRC, WHO), spirometry, chest x-ray, physical examination
Jancik, 1968	230	Brno	Urban		2736 men	40 to 64	Mailed and MRC questionnaires, FEV ₁ , FVC, PFR, chest x-ray (inspiratory/expiratory PA, inspiratory/lateral)
Boudik <i>et al.</i> , 1970	231	Prague	72.8%	All men in area of Prague 2	8292	50 to 65	MRC questionnaire, FEV ₁ , FVC, PEFR
The Netherlands Van der Lende, 1968	24	Meppel Vlaagtwedde Vlaardingen	Rural Urban	Random samples	3798 men 1604 women	40 to 64	MRC questionnaire, FEV ₁ , FVC, bronchial reactivity, etc.

Table 13 (continued). EUROPEAN STUDIES OF THE PREVALENCE OF CHRONIC OBSTRUCTIVE LUNG DISEASES

Author and year	Reference	Area	Population	Sample, type and % of population	Number surveyed	Age range, years	Methods
The Netherlands (continued) Biersteker, 1969	232	Rotterdam	Urban	Male municipal employees	1000	30 to 64	NCB questionnaire, PFR
Italy Petrilli <u>et al.</u> , 1966	233	Genoa: Industrial residential, and suburban areas Ferrara	Urban	Women non-smokers who had never worked in industry Elementary school children	313	>65	MRC questionnaire, morbidity
Paccagnella <u>et al.</u> , 1969	234		All children in three schools in appropriate age		385	7 to 12	Daily examination to detect onset of acute respiratory disease

FACTORS IN THE ETIOLOGY OF CHRONIC RESPIRATORY DISEASE

AGE, SEX, AND RACE

Mortality and Morbidity Rates

In nearly all countries, the age-adjusted and age-specific mortality rates for chronic respiratory diseases are higher in men than in women. In adult life, the mortality rates increase with age in both sexes. In many countries, however, the rate of increase is greater in men than in women.^{15,16,82} In England and Wales, for example, the sex ratio of mortality from chronic bronchitis at all ages for men and women is 3 to 1 at ages 35 to 44, 9 to 1 at ages 65 to 74, and about 5 to 1 for all age groups (Table 14).

Table 14. MORTALITY RATES BY SEX FOR CHRONIC BRONCHITIS AND OTHER CHRONIC RESPIRATORY DISEASES IN MALES AND FEMALES IN THE UNITED STATES, 1967^a

Age group, yr	Chronic bronchitis (A 93) ^b			All other respiratory diseases (A 97)		
	Males	Females	Ratio	Males	Females	Ratio
0	4.9	2.9	1.7	42.0	35.1	1.2
1-4	0.6	0.4	1.5	1.5	1.0	1.5
5-14	0.1	0.1	1.0	0.3	0.3	1.0
15-24	0.1	0.1	1.0	0.5	0.3	1.7
25-34	0.1	0.2	0.5	1.0	0.7	1.4
35-44	0.5	0.3	1.7	3.4	1.9	1.8
45-54	2.5	1.0	2.5	15.2	5.4	2.8
55-64	9.9	2.5	4.0	67.6	12.6	5.4
65-74	26.3	4.7	5.6	182.6	23.8	7.7
≥ 75	45.7	10.7	4.3	269.1	55.1	4.9
All ages	4.2	1.3	3.2	27.0	6.7	4.0

^aDeaths/100,000 population.

^bNumber in parentheses is the International Statistical Code.

Crofton and Crofton²⁴⁰ studied changes in the sex ratio in respiratory disease mortality in England, Wales, and Scotland by studying mortality rates from those diseases that are possibly connected with smoking in cohorts born between 1846 and 1855 and between 1896 and 1905. The results suggest that smoking has been exerting an effect on mortality longer in England and Wales than in Scotland. The

recent rise in mortality from bronchitis that has been noted in Scotland⁷⁰ could be the result of smoking, which is now beginning to exert an influence there on the death rates of middle-aged men.

Most morbidity surveys have shown a clearly excessive prevalence of cough and sputum in men compared with women. 24, 52, 96, 199, 206, 215, 224 Much of the sex difference for these symptoms is probably the result, however, of differences in smoking habits. 24, 241 Wheezing in the chest follows a somewhat similar pattern,²⁴ but chest illness during the past 3 years has usually been found to be equally prevalent in men and women. 24, 206, 215, 224 Breathlessness has been either equally prevalent in the two sexes or more frequent in women. 24, 211, 228

Findings on the relationship between age and respiratory morbidity have been less consistent. Some surveys have shown the persistent cough and sputum increase with age, 80, 96, 111, 215, 242, 243 but others have found little increase with age in the prevalence of these symptoms, 199, 206, 224 except that most studies have shown a consistent increase in the prevalence of breathlessness. 24, 80, 96, 211, 215, 244 The trend is often less consistent in women than in men. The prevalence of the other symptoms, namely, chest illness in the past 3 years and wheezing in the chest, are somewhat inconsistently related to age. Whether an increase in the prevalence of chronic respiratory disease with increase in age is noted or not clearly depends to some extent, therefore, on the diagnostic criteria used. When breathlessness is included, an age-related trend is likely to be noted; when only cough and sputum are used, there may or may not be an age-related trend. Cough and phlegm and, to a lesser degree, wheezing in the chest, are determined mainly by smoking habits; the other symptoms, though apparently influenced to a slight extent by cigarette smoking, are determined mainly by other factors. Cough and phlegm, however, may also be a manifestation of air pollution when the pollution is severe enough. For example, Holland and his colleagues²¹⁹ noted a clear relationship between age and the prevalence of cough and sputum in London, but a relationship was much less apparent in persons living in country towns in England or in cities in the United States.

Attention has already been drawn to the differences in overall mortality rates for respiratory diseases between whites and nonwhites in the United States. Metropolitan Life Insurance records show that the death rates from chronic bronchitis and emphysema for 1958 through 1961 were lower in black male than in white male industrial policy holders.²⁴⁵ A racial difference in incidence of chronic bronchitis has been suggested by Massaro and his colleagues on the basis of findings in United States' veterans admitted to hospitals.^{246, 247} Thus, in a review of 964 patients admitted to the Veterans' Administration Hospital, Washington, D. C., Massaro and his colleagues²⁴⁶ showed that the prevalence of bronchitic symptoms was lower in black than in white persons. The difference was due in part to the lower proportion of smokers among the blacks. Among nonsmokers, however, the prevalence of bronchitis among the blacks was still half that of the white nonsmokers. In the largest study in which race has been considered, Densen and his colleagues²⁴⁴ studied 12,604 male New York transport and postal workers. The study revealed a lower prevalence of respiratory symptoms and bronchitis among the black workers than among the white. Among nonsmokers, however, there was little difference between the two races in the prevalence of symptoms. This would suggest the possibility that most of the racial differences in symptom prevalence can be explained by differences in smoking habits.

Lung Function Levels

The influence of age and sex on the forced expiratory volume test is fairly clear. Many studies have shown that from about the age of 25 there is a fairly uniform decline in FEV with increasing age. Although some studies have suggested that the decline is not linear, most observations have indicated that any deviation from such a trend with age is not marked and that for practical purposes a linear decline can be accepted as occurring. A number of studies in which the forced expiratory volume was used have been reviewed by Cotes and his colleagues.¹³¹ The similarity in the age trends in more or less comparable groups studied in the United Kingdom, United States, and Europe is striking. Cotes and his colleagues combined a number of surveys and presented an overall regression for use in predicting normal values, taking age and height into consideration. The regression is:

$$FEV_{1.0} = (3.62 \times \text{height}) - (0.031 \times \text{age}) - 1.41 \text{ (SD } \pm 0.5 \text{) (l BTPS)}$$

where height is in meters, age is in years, and the final factors are corrections for standard deviation and body temperature and pressure saturated with water vapor. A summary of the regression relationships between FEV and age and height that were found in different surveys and used to derive this equation is given in Table 15.

Table 15. REGRESSION RELATIONSHIPS OF FEV_{1.0} ON AGE AND HEIGHT¹³¹

Survey sample	Height, m	Age, yr	Constant
Veteran's Administration United States	3.70	-0.028	-1.59
Berlin, New Hampshire United States	3.60	-0.027	-1.65
Goteborg, Sweden	3.75	-0.036	-1.09
Pneumoconiosis Research Unit United Kingdom	3.46	-0.033	-1.12

The FEV in women is approximately 75 percent of that found in men of the same age.^{24, 206} Most of the difference is attributable to the shorter height of women. Some of the residual difference in the overall regression of FEV on age between men and women when height is held constant is attributable to cigarette smoking. Occupational exposures also appear to influence the level and slope of the regression in men in some areas.²⁴⁸

A lower vital capacity in black children compared with children of other races was observed early in this century. Thus, in 1922, Wilson and Edwards²⁴⁹ found that in children aged 8 to 14 years the vital capacity was strikingly lower in blacks than in other groups. In 1950, Roberts and Crabtree²⁵⁰ also found that the vital capacity was lower in black than in white children of the same age and that the difference was greater for boys than for girls. In adults, a low vital capacity in blacks was noted more recently by Nahmias and his colleagues.²⁵¹

Gilson and his colleagues,²⁵² in a survey of cotton ginneries in Africa, noted that the average forced expiratory volume was at least 0.5 liter lower in Africans than would have been expected for Europeans of the same age. About half the

difference was attributable to shorter sitting height, but the remaining difference was unexplained.

Abramowitz and his colleagues²⁵³ examined normal hospital employees and resident and full-time physicians of the Veterans' Administration Hospital, East Orange, New Jersey. In males, both the FEV_{1.0} and the FVC were lower in blacks. In females, though the differences were in the same direction, they were not statistically significant; however, the white women were 4 years older than the black women and the differences observed are therefore smaller than the true differences between the two groups.

In a comparison of 392 white and 61 black soldiers aged 18 to 29 years, Damon²⁵⁴ noted that the black soldiers had a 13 percent smaller 1-second and total vital capacity and a 10 percent slower midexpiratory flow rate, even though the white soldiers smoked more. The differences could not be explained by shorter trunk and smaller chest expansion of the blacks. Damon observed that differences of this magnitude had been reported for almost 100 years and that they were not attributable to prior pulmonary disease.

In Densen's study in New York City,²⁵⁵ the forced expiratory volume was lower in black than in white persons and the difference persisted after adjustment for sitting height. The rate of decline also appeared to be different in white and black men. Thus, in men under 35 years of age, the average FEV was 0.30 liter greater in whites than in blacks; but in men aged 60 and over, the difference was only 0.05 liter.

GENETICS AND PHYSIOLOGY

Heredity

In the early study carried out by Oswald and his colleagues,²⁵⁶ a higher proportion (about threefold more) of first-degree relatives of bronchitis patients than of controls were reported as having bronchitis. Similarly, Ogilvie and Newell,¹⁷ who studied bronchitis in Newcastle, England, found that twice as many parents and sibs of bronchitics were reported to have bronchitis compared with the relatives of controls. The importance of a family history of bronchitis was also noted by Clifton in Sheffield.²¹⁶ Since the diagnosis of bronchitis in the relatives was based on history taking, the possibility that bronchitis patients remember and recall relatives who have bronchitis better than those who do not cannot be excluded.

Layland²⁵⁷ made an attempt to assess the importance of heredity by comparing the experience of wives and sisters of men with and without bronchitis. Patients admitted to hospitals or attending hospital clinics were used. Among the relatives of men without bronchitis and with a normal FEV, 4.5 percent of the wives and 2.25 percent of the sisters were found to have bronchitis. Among the relatives of men with bronchitis, the corresponding frequencies were 6.0 and 21.5 percent, respectively. Since men probably know the symptoms of their wives better than those of their sisters, the findings were considered to indicate a familial tendency. The possibility that a similar environment in childhood could explain the findings prevented the author from concluding that this familial tendency was genetic.

Familial Aggregation

Familial aggregation of chronic obstructive lung disease has been noted by Larson and Barman,²⁵⁸ who showed that the relatives of a small number of bronchitis patients had a history of a higher prevalence of cough and dyspnea and had a lower ventilatory capacity than the relatives of patients with miscellaneous nonobstructive pulmonary disease.

Disease among Twins

Studies of twins based on the Swedish twin registry and, more recently, on the United States veterans' registry were carried out by Cederlof and his colleagues, 114-117,²⁵⁹ who collected the information by mailed questionnaires. The validity of the questionnaire method with regard to the determination of zygosity, smoking habits, and medical information had been tested on subgroups and was considered adequate by the authors. Cough was used as an index of respiratory disease. People were classified into those with "cough" and those without, according to their answer to the question: "Do you regularly have a cough, or do you at least have a cough for long periods at a time?" Those who also said that this "cough" lasted for 3 months or more in succession were classified as having "bronchitis." "Bronchitis" was apparently only one-fourth as prevalent as "cough," namely, 2 percent compared with 8 percent. The concordance rates for cough among nonsmokers were higher in the monozygotic than in the dizygotic pairs. The rates were higher in women than in men and in younger persons than in older. The authors concluded that this indicates a genetic influence on the development of the symptom. Furthermore, through comparison of the prevalence of cough or "bronchitis" found in monozygous twin pairs--who differed with respect to such factors as smoking or urban or rural residence--with the appropriate values for the general population, an estimate was obtained of the relative importance of heredity and environment in the production of such symptoms. Such analyses indicate that smoking is more likely than genetic predisposition to cause cough.

Familial Emphysema

In 1959, Hurst²⁶⁰ studied two families in which emphysema was a major disabling problem. He reviewed the earlier literature on the subject and stressed the difficulty of differentiating genetic factors from those resulting from cross-infection. He concluded, however, that a familial tendency was likely.

Hole and Wasserman²⁶¹ described a case of familial emphysema with a pedigree dating back approximately 150 years. The disease appeared to follow the familial distribution of an autosomal dominant trait having variable phenotypic expression. Neither cystic fibrosis nor an autoimmune mechanism were thought to be likely explanations for the aggregation.

Mucoviscidosis

The possible role of mucoviscidosis in chronic respiratory disease has been investigated. Karlisch and Tarnoky²⁶² examined the electrolyte content of sweat and found it to be abnormally high in a large proportion of patients with chronic respiratory disease. The possibility that heterozygosity for the mucoviscidosis trait might play a role was suggested; however, further studies have failed to support the original observation.²⁶³⁻²⁶⁸ Furthermore, Hallett and his colleagues²⁶⁹ have

shown that persons who are heterozygous for the mucoviscidosis trait are no more liable than others to respiratory disease; nor does their perspiration contain higher concentrations of chloride.

Alpha₁-antitrypsin Deficiency

Deficiency of a serum protein, alpha₁-antitrypsin, may lead to the development of chronic obstructive lung disease at a relatively early age.^{264,267,270-274} The characteristic features of the disease are an early onset, a family history of pulmonary disease, often involving women, and, frequently, an absence of a history of chronic bronchitis. Abnormal lung function has been shown to occur in persons who have the deficiency but who have no symptoms.²⁷⁵

Alpha₁-antitrypsin deficiency is found in less than 2 percent of all cases of severe emphysema. It seems unlikely, therefore, that it is a very important factor in the development of most cases of chronic obstructive lung disease. It has been suggested, however, that up to 7.5 percent of the American population may be heterozygous carriers of the deficiency gene.²⁷⁶ Some studies suggest that the incidence of chronic obstructive lung disease may be increased in such carriers.²⁷⁷⁻²⁷⁸ At least one study has failed to support this suggestion.²⁷⁹ It seems clear that further observations are needed on samples more representative of the population than those that have been studied to date.

Blood Groups and Secretory Function

Blood-group frequency in patients with six respiratory disorders were studied by Lewis and Woods²⁸⁰ at the Brompton Hospital in London. They found no evidence of any association between blood group and cases diagnosed as bronchitis and emphysema. Higgins and his colleagues²⁸¹ investigated A, B, O, and Rhesus blood groups and secretor status in an age-stratified sample of miners and ex-miners living in a Welsh mining valley. They found no evidence that these factors were related to chronic respiratory disease.

AIR POLLUTION

The main types of epidemiological studies conducted to assess the effects of air pollution are summarized in Table 16.

Acute Episodes

Acute episodes of high pollution, such as those that have occurred in the Meuse Valley, Belgium;²⁸² Donora, Pennsylvania;²⁸³ London;²⁸⁴ New York City;²⁸⁵ Osaka, Japan;¹⁷⁷ and elsewhere provide the most convincing and dramatic evidence for an effect of air pollution on health.

From December 5 to 8, 1952, dense fog covered the Greater London area. During the following week, death rates reached a level that had been exceeded only rarely during the preceding 100 years, in the cholera epidemic of 1854 and the influenza epidemic of 1918-1919, for example. It was subsequently estimated that approximately 4000 deaths were attributable to the fog. Persons of all ages were affected but particularly those aged 45 years and over. There was an eightfold increase in deaths attributed to bronchitis, a threefold increase in deaths from pneumonia, and a considerable increase in deaths caused by other respiratory and

Table 16. MAIN TYPES OF EPIDEMIOLOGICAL INVESTIGATIONS
OF EFFECTS OF AIR POLLUTION ON HEALTH

Specific studies
Follow-up of Donora, Pennsylvania, episode
Study of Yokohama and New Orleans asthma
General types of studies
Variation in mortality, morbidity, and lung function over time
Day-to-day variation in residents of large cities
Day-to-day variation in patients with respiratory disease
Long-term changes in lung function
Geographical comparisons
International
Regional
Urban-rural
Uniform occupational groups
Comparisons between cities
Comparisons within cities
Studies of children
Miscellaneous studies
Migrants
Twins
Athletes

cardiac diseases. Morbidity also increased, as shown by claims for sickness benefit received by the Ministry of Pensions and National Insurance, applications for admission to hospitals through the Emergency Bed Service Bureau, notification of pneumonia, and the observations of interested general practitioners on the number of new cases seen during the episode compared with those occurring at other times.^{287,288} Lethal fogs in London were documented for the years 1873, 1880, 1882, 1891, 1892, and 1948,²⁸⁹ and several similar fogs have occurred in London and in other British cities since 1952.²⁹⁰⁻²⁹⁵ At the height of the pollution in London in 1952, the concentration of smoke was 4.46 milligrams per cubic meter and that of sulfur dioxide (SO_2) was 1.34 parts per million (2.86 milligrams per cubic meter). The maximum smoke concentrations at individual sites were 3 to 12 times the normal values, while the maximum concentrations of SO_2 at individual sites were between 3 and 10 times normal.²⁹⁶ Burgess and Shaddick²⁹¹ reviewed some of the difficulties encountered in relating mortality to levels of air pollution and suggested that in London a smog episode was likely to occur when smoke concentrations rose above 2000 micrograms per cubic meter and SO_2 concentrations rose above 0.4 part per million (1144 micrograms per cubic meter).

Episodes of pollution have also been responsible for increased mortality and morbidity in New York City,^{285,286,297-300} but these appear to have been considerably less lethal there than in London. Thus in the episode in New York in 1953,

it was estimated that there were about 200 excess deaths; in 1963, between 200 and 400; and, in 1966, 163 excess deaths. In New York City, episode-related deaths have been attributed to influenza, pneumonia, vascular lesions of the nervous system, cardiac diseases, and "all other diseases." Those aged 45 years and over have been predominantly affected. Increased morbidity, particularly for upper respiratory and cardiac disorders, and sometimes for asthma, was noted as a result of studying emergency visits to a number of hospitals. In a study carried out at the time of the Thanksgiving holiday fog in 1966, Becker and his colleagues³⁰¹ showed that as pollution levels rose, complaints of cough, sputum, wheezing, breathlessness, and eye irritation increased.

The increased mortality and morbidity that have occurred in these acute episodes of pollution probably affected predominantly those who already were suffering from some chronic illness, particularly of the heart or lungs. Evidence, however, that fog may initiate illness as well as exacerbate it is provided by the descriptions of effects on animals during several episodes of fogs. In both the Meuse Valley episode and the London fog of 1952, cattle sickened and some died, while in Donora, ten dogs, three cats, and two canaries were reported to have died.

There is little doubt that these exceptional episodes of high pollution may cause mortality and morbidity, but much more uncertainty exists about the effects of lower, more sustained levels of pollution and their long-term effects.

In 1948, immediately after the disaster in Donora, Pennsylvania, a probability sample of the inhabitants of the town was studied by the United States Public Health Service.²⁸³ Ten years later, Ciocco and Thompson³⁰² followed up this sample and found that the group who had reported being affected by the fog had higher mortality and morbidity during the next 10 years than those who had not been affected. Most of the excess, however, was in persons who had reported having chronic illness before the fog. This suggests that the fog mainly exacerbated existing disease rather than initiated illness. Even among those with no prior chronic illness in 1948, however, mortality rates were slightly but consistently higher in persons who had been affected by the fog. The authors of the study also compared the prevalence of heart disease, asthma, and arthritis and rheumatism in survivors of the 1948 Donora episode with that found in residents of two neighboring Pennsylvania communities. They found little difference between the groups. They concluded, therefore, that the fog appeared to have had little effect on the prevalence of these diseases. In view of the excess mortality over the 10 years in those who had reported being affected by the fog, a lower prevalence among the Donora survivors might perhaps have been expected. The equal rate of prevalence found might therefore reflect some increase in disease frequency.

Variation in Mortality, Morbidity, and Lung Function with Time

Daily measurements of smoke and sulfur dioxide have been related to daily deaths and illnesses in London since 1958. The aim has been to establish a dose/response curve, and, particularly, to determine the maximum acceptable levels of these pollutants. The deviation in the number of deaths or illnesses from a 7- or 14-day moving average is used. Mortality and morbidity for all causes and for certain respiratory diseases were rather highly correlated with both smoke and SO₂ levels until 1962; but since 1962-1963 there has been little evidence of any effect of pollution on mortality or morbidity.³⁰³ It seems reasonable to attribute this change to the great reduction in pollution that has been achieved in London

during the past 10 years. During this period the annual smoke concentrations have fallen from about 300 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) to about 60 $\mu\text{g}/\text{m}^3$, and from about 250 $\mu\text{g}/\text{m}^3$ to 175 $\mu\text{g}/\text{m}^3$.³⁰³

Fletcher and his colleagues^{107,190} made regular observations on 1000 men aged 30 to 59 living in North London from 1961 to 1966. The incidence of respiratory illnesses (coryza, chest colds, mucopurulent bronchitis, wheezy attacks, "flu," or acute respiratory disease) were found to be related to both smoke and sulfur dioxide levels. During the period of observation the volume of morning sputum produced by the men under observation declined. This could have resulted from the concurrent reduction in air pollution, but it might also have resulted from a reduction in the tar content of cigarettes, which occurred at the same time. It is interesting to note in this connection that Waller and his colleagues³⁰³ observed a progressive improvement in peak expiratory flow rates in four trained subjects between 1960 and 1965.

In New York City, day-to-day studies of mortality have indicated that periodically there are days when high pollution levels occur in association with unexpectedly high mortality rates.^{300,304} The increase in deaths occurs immediately after the pollution levels rise. It is usually followed by a drop below the expected number of deaths the following day, but the decrease is never sufficiently large to compensate for the excess deaths. Consequently, these deaths are not thought to occur only among those with terminal illnesses.

McCarroll and his colleagues³⁰⁵ followed a segment of the population of Manhattan Island for a 2-year period, during which information on 25 symptoms was reported daily by 1860 people. Even more information was collected by weekly interviews. The findings in 1090 persons indicated that complaints of cough and eye irritation were correlated with increases in levels of SO_2 and particulates.

In an attempt to study a more susceptible group of people, Lawther and his colleagues^{303,306-310} made observations on bronchitis patients. Each patient kept a daily record in a pocket diary of changes in his health by recording whether his chest was better, worse, or the same as usual. A close correlation between the concentrations of smoke and SO_2 and the clinical condition of the patients was first noted during the winter months. In the earlier years of the study (1959-1960), the correlations were higher than 5 years later (1964-1965), when the concentration of smoke in London had been considerably reduced. The patients appeared to be most sensitive to changes in pollution early in the winter. The minimum pollution level leading to a significant response was about 500 $\mu\text{g}/\text{m}^3$ SO_2 and about 250 $\mu\text{g}/\text{m}^3$ smoke.

In studies of bronchitic patients carried out in Chicago by Burrows and his colleagues,³¹¹ the severity of symptoms in bronchitic patients appeared to vary with temperature and SO_2 level. If season and daily temperature were held constant, however, only hydrocarbon levels showed an independent correlation with symptoms. The authors concluded that air contaminants did not appear to play a major role in the daily variation in the patients' symptoms; however, Carnow and his colleagues,³¹² who also studied patients in Chicago, showed that in certain groups of bronchitic patients there was an increase in illness with increase in SO_2 concentrations.

Physiological measurements of lung function have been included in some studies of the effects of air pollution on respiratory disease. For example, Bates and

his colleagues^{313, 314} carried out repeated tests of lung functions in Canadian veterans with chronic bronchitis (in Winnipeg, Montreal, Halifax, and Toronto). They observed that the veterans in Winnipeg were less severely affected and had better lung function--which declined less during the period of observation--than veterans in the other cities. Winnipeg is the least polluted of the four cities. Whether the differences observed were caused by the differences in pollution or by other factors, such as selection of patients, is, however, uncertain.

Changes in lung function in relation to pollution were studied in small groups of patients with respiratory disease by Spicer and his colleagues.³¹⁵ Results of the lung function tests indicated that the patients tended to vary as a group, which suggested the influence of some common environmental factor. In a later paper,³¹⁶ temperature, wind speed, barometric pressure, and SO₂ levels appeared to be the most important factors influencing lung function in these patients. Certain changes in lung function in cardiorespiratory cripples were attributed to concentrations of suspended particulates in reports by Shephard and his colleagues.^{317, 318}

Insurance records and absence from work as a result of illness have often proved to be useful indices in studies of the effects of air pollution.³¹⁹⁻³²³ For example, industrial absenteeism caused by upper respiratory tract infections was related to air pollution in Philadelphia by Ipsen and his colleagues.³²¹ Workers in the Camden plant of the Radio Corporation of America and in the Curtis Publishing Company were studied from 1960 to 1963. High respiratory morbidity was found to be preceded by a week in which air pollutants exceeded their normal seasonal level. It was also found to be associated with seasonably low temperature, high humidity, and higher than normal wind velocity.

Sterling and his colleagues^{322, 323} studied hospitalization in relation to air pollution using records from Blue Cross and Blue Shield of Southern California. They found that admission to the hospital and duration of stay for diseases and other conditions that they categorized as relevant to air pollution were significantly correlated with pollutant levels, including levels of sulfur dioxide. These findings are surprising in that the average level of SO₂ in the air during the period of study was around 13 parts per billion (37 µg/m³). It is difficult to believe that concentrations in this range can exert much effect on health.

Geographical Differences

Because air pollution gradients exist within and between cities, rural areas, and even countries, comparative studies constitute one means of studying the effects of air pollution on health.

International differences - The large differences in bronchitis mortality between different countries have sometimes been attributed to differences in pollution between them, but it has become increasingly clear that diagnostic practices differ in different countries and that variations in death certification account for much of the variation. When these are allowed for, however, differences in mortality and morbidity still exist between different countries.^{78, 80, 81, 324, 325} Some of these differences could be the result of differences in air pollution levels.

Some of the difficulties inherent in carrying out international comparisons are indicated by the studies conducted by Ferris and Anderson.³²⁴ These authors

compared respiratory disease and lung function in representative samples of the inhabitants of two towns that differed in their degree of air pollution. In 1961 they studied one of each 10 adults living in Berlin, New Hampshire. Two years later, in 1963, they carried out a comparable study of one in each seven inhabitants aged 25 to 74 of Chilliwack, British Columbia. In each survey, methods were comparable and the observers the same, thereby largely eliminating one major cause of differences between surveys. Information about respiratory symptoms and smoking habits was obtained using a prototype of the British Medical Research Council's respiratory symptoms questionnaire. Forced expiratory volume (FEV) and peak expiratory flow rate (PEFR) measurements were used to assess ventilatory lung function. On the basis of the age-specific prevalence of symptoms in both surveys, expected rates for nonsmokers were calculated, while from the multiple regression equations on age and height for FEV and PEFR for Berlin, expected lung function values were calculated for Chilliwack. Respiratory disease prevalence for male nonsmokers differed little from that expected, but in women the prevalence was slightly below expectation. Lung function values were also consistently slightly higher than expected in both men and women in Chilliwack for all smoking categories. These differences are in the direction one would expect if pollution were exerting an effect. As the authors point out, however, differences could be the result of ethnic differences between the two populations.

The possibility that international differences in chronic respiratory disease mortality might be attributable to different opportunities for contracting respiratory infections was the basis of a study carried out by the MRC on the respiratory experience of students from abroad who were attending British universities.³²⁶ It was thought that students from other countries might experience a higher incidence of respiratory infections from British microbiological flora than students who were accustomed to such infectious agents. No evidence was obtained to support this hypothesis. The findings were, in fact, just the opposite; namely, that the British students under 25 years had a higher frequency of colds, especially of more severe colds, than the overseas students of the same age had.

Urban-rural Differences - A striking feature of the mortality statistics of certain countries is a pronounced gradient in death rates for chronic respiratory disease between urban and rural areas. This trend is pronounced in the United Kingdom for both men and women. In the United States, a similar though much less impressive trend has been observed for men but not for women.⁸⁷ These observations have stimulated a great deal of research. In the earliest of such studies, mortality rates in different areas were related to levels of air pollution where pollution data were available.³²⁷⁻³³³ Mortality from bronchitis was found to be correlated with indices of pollution, social circumstances, and density of population. More recently, urban-rural differences in bronchitis mortality have been demonstrated in male and female nonsmokers.^{332, 333} A pronounced urban-rural gradient of bronchitis symptoms, comparable to the gradient that exists for bronchitis mortality, was shown in a survey of a random sample of men and women who were patients of 92 general practitioners in Britain.²¹⁸

In 1961 and 1962, a nationwide study, "Enquiry into the Incidence of Incapacity," was carried out in the United Kingdom.⁹¹ The incidence of incapacity for work in different areas and among different occupations in random samples of all employed men and women was studied. Incapacity because of bronchitis was found to be significantly correlated with ambient concentrations of smoke and sulfur dioxide in each of four 10-year age groups.³³⁴ The interpretation of the findings is, however,

somewhat uncertain because similar correlations were also observed between the levels of these pollutants and arthritis and rheumatism. This suggests that differences in factors other than pollution levels may also have been present, one of the more likely of which is social class.

Intercity Differences - Comparisons have sometimes been made among towns having different levels of air pollution. Dohan and Taylor^{335, 336} related claims for insurance benefits for female employees of Radio Corporation of America to levels of pollution in five cities. They found a high correlation between respiratory illnesses of 7 days' duration or more and average levels of suspended particulate sulfates for the years 1955, 1956, and 1957. Age distribution, conditions of work, and social and climatic factors did not appear to account for the observed fivefold variation in the incidence of these illnesses in the cities.

A comparison of respiratory disease and lung function in two towns in Pennsylvania that had contrasting levels of air pollution was carried out by the United States Public Health Service.²⁰³ Average dustfall in Seward, the more polluted town, was 3.2 times and SO₂ was 6.2 times that of New Florence. Age- and height-adjusted mean values of most of the lung function tests were considered by the investigators to be remarkably similar in the two towns. Values for airway resistance times volume were the only statistically different results; each was higher in Seward than in New Florence. Nevertheless, there were also small but consistent differences in maximum breathing capacity, 1-second forced expiratory volume, and maximum mid-expiratory flow, each value being lower in Seward. It is difficult to attribute these physiological differences solely to the greater air pollution in Seward because there were other differences between the two towns (for example, Seward's population included a higher proportion of coal miners.)

Intracity Differences - Differences in mortality and morbidity often occur in different areas of a single large city. It is sometimes possible to correlate these with differences in air pollution. In London, Reid^{337, 338} showed that the mortality and morbidity of postmen were related to an index of pollution based on fog frequency. The study subsequently carried out by the Ministry of Health, along with other studies, supported and extended these findings.^{91, 319, 320}

Burn and Pemberton³¹⁹ studied morbidity and mortality in relation to pollution in Salford, England, for the years 1958 and 1959. They noted a twofold or greater increase in new attacks of bronchitis during four out of five smog episodes. They also noted that mortality and morbidity rates from bronchitis were higher in more polluted areas of the city than in less polluted areas. They were not, however, able to exclude the possibility that overcrowding or other social factors could have been responsible. Nor were they able to exclude a relationship between smoking and bronchitis because their study included no data on smoking habits.

In the United States, studies correlating mortality rates with levels of pollution in different parts of the city were carried out in Buffalo, New York.^{339, 340} Pollution in Buffalo was monitored from 1961 to 1963 and particulate levels and sulfation rates were related to mortality for 1959 to 1961. Total mortality rates for men and women aged 50 years and over and respiratory disease mortality for men 50 to 69 were both significantly correlated with suspended particulate concentrations (Table 17).³³⁹ There was also a correlation between sulfation and mortality rates for chronic respiratory disease for men aged 50 and over.

One of the most detailed studies of air pollution was conducted by the United States Public Health Service in Nashville, Tennessee, ³⁴¹⁻³⁴³ where pollution was monitored by a network of 123 stations. Mortality rates from 1949 to 1960 were correlated with pollution levels. Age-specific death rates for respiratory disease for ages 25 to 74 were directly related to sulfation levels and cardiovascular mortality was related to soiling by particulate pollution. Various indices of morbidity, such as the frequency of asthma attacks, have also been related to pollutant levels in Nashville.

Unfortunately, in neither Buffalo nor in Nashville was attention directed to smoking habits or to occupation. More recently, however, Winkelstein and Kantor ³⁴⁴ have studied the relationship of respiratory symptoms to air pollution in a random sample of white women in Buffalo. They found that among nonsmokers aged 45 and over there was a positive association between cough and phlegm and suspended particulate levels. There also appeared to be a relationship between residential mobility and respiratory symptoms among smokers. Among smokers who did not change residences, cough and sputum were positively correlated with air pollution at the place of current residence; but among those who had moved within the past 5 years there was a negative association. The associations found were not attributable to social class. No association was found between sulfur oxide levels and respiratory symptom prevalence.

Table 17. MEAN ANNUAL MORTALITY RATES FROM ASTHMA, BRONCHITIS, OR EMPHYSEMA^a
BY ECONOMIC STATUS AND POLLUTION LEVEL FOR WHITE MALES AGED 50 to 69
YEARS IN BUFFALO, NEW YORK, 1959 to 1961^b
(deaths/100,000)

Median family income, \$	Mean annual particulate concentration, $\mu\text{g}/\text{m}^3$			
	≤ 80	≥ 80	≥ 100	≥ 135
3005 to 5007	--	126	271	392
5175 to 6004	136	154	172	199
6013 to 6614	--	74	110	128
6618 to 7347	70	80	177	--
7431 to 11,792	79	109	0 ^c	--

^aBased on appearance anywhere on death certificate of asthma, bronchitis, or emphysema.

^bAdapted from Winkelstein. ³³⁹

^cRate based on fewer than 5 deaths.

One of the most interesting studies of the effects of pollution in different parts of a town was conducted in Genoa, Italy, by Petrilli and his colleagues. ²³³ Genoa is a rapidly growing industrial city situated between the Appennines and the Mediterranean. As a result of Genoa's topography, the local climate may differ strikingly in different parts of the city. From 1954 to 1964, pollution was assessed at 19 sites. Sulfation rates, SO_2 , carbon monoxide, lead, dustfall, and suspended particulates (estimated gravimetrically and by particle size), and 3,4-benzpyrene were monitored. Mean values for available data from 1962 to 1964 showed an increase of about 20 percent over 1954 to 1961. Respiratory symptoms were studied

in nonsmoking women aged 65 years and over who had not worked in industry but who had resided for a long period in the same area. The results were also analyzed by floor level (height above ground level) of residence. Strong associations were shown between the frequency of respiratory disease and the concentration of SO₂. Annual morbidity rates for bronchitis and other respiratory diseases (1961 and 1962) in seven districts where air pollution was measured continuously also showed that these varied with the average annual SO₂ concentrations. Unfortunately, analysis of the data was inadequate to permit a firm judgment about the effectiveness with which the authors standardized for socioeconomic factors.

Disease among Homogeneous Occupational Groups

To obviate the confounding of differences in exposure to air pollution with differences in social class, Fairbairn and Reid³⁴⁵ studied British postmen, a homogeneous occupational group who receive the same pay wherever they work and who, once established, tend to remain in the same area. They found that premature retirement and death from bronchitis and pneumonia were related to thick and presumably polluted fog and were independent of domestic overcrowding or population density. Somewhat similar observations have been made of British transport workers.³⁴⁶

In this country, special surveys of Bell Telephone employees have been carried out by Holland and his colleagues²¹⁰ and by Deane and her colleagues.²⁰⁸ The results have been compared with studies carried out in a comparable manner in London and smaller towns in England.²¹⁹ Differences in symptom prevalence, morning sputum volume, and lung function were observed that were in the direction to be expected if pollution were playing a role.

Disease among Children

Studies by Reid^{325, 347} have shown the value of studying children to elucidate the effects of pollution on health; children are particularly suitable because they are usually nonsmokers and for the most part are not occupationally exposed to high dust levels. They may also be exceptionally sensitive to the effects of pollution. Wahdan³⁴⁸ compared children in Sheffield, England, a polluted city, with children living in the Vale of Glamorgan, an area of unpolluted countryside. He found that the frequency of sinus opacity and otitis media was higher in Sheffield.

In Japan, Toyama³⁴⁹ and Watanabe^{177, 239} found that school children living in Kawasaki and Osaka, two polluted cities, had lower peak expiratory flow rates than children living in less polluted areas. One of the more interesting studies of children was carried out in Britain by Douglas and Waller, who initiated a study of child health and development in 1946. A longitudinal study of all children born in a 1-week period in March 1946 was conducted until the children left school at age 15. Subsequently, the illness experience of the children was related to the areas in which they had lived and thus to the probable levels of pollution experienced through life. The results showed that lower respiratory tract infections were consistently related to pollution (Table 18) but that upper respiratory tract infections were not. Both the frequency and severity of such infections increased with the amount of pollution. The lowest levels of smoke and SO₂ observed were 67 µg/m³ and 90 µg/m³, respectively. In all cases, higher illness rates were noted for the higher pollution levels.

Table 18. FREQUENCY BY POLLUTION LEVELS OF LOWER RESPIRATORY TRACT
INFECTIONS IN BRITISH CHILDREN^a
(percent)

Lower respiratory tract infections	Mean annual pollutant concentration, $\mu\text{g}/\text{m}^3$			
	Part. = 67 SO ₂ = 90	Part. = 132 SO ₂ = 133	Part. = 205 SO ₂ = 190	Part. = 190 SO ₂ = 251
First attack within first 9 months	7.2	11.4	16.5	17.1
At least one attack within first 2 years	19.4	24.2	30.0	34.1
More than one attack within first 2 years	4.3	7.9	11.2	12.9
Boys	5.7	8.1	10.9	16.2
Girls	2.9	7.7	12.1	9.7
Middle class	3.0	4.0	7.7	9.3
Manual working class	5.1	10.8	13.9	15.4
Cause of admission to hospital within first 5 years				
Lower respiratory infection	1.1	2.3	2.6	3.1
Bronchitis	0.0	0.9	1.0	1.4
Pneumonia	1.1	1.4	1.6	1.8

^aAdopted from Douglas and Waller.³⁵⁰

An interesting piece of evidence supporting the importance of home residence in early life to susceptibility to respiratory disease was found by Rosenbaum,³⁵¹ who correlated respiratory disease incidence in national servicemen with their home localities. Prior residence in industrial areas seemed to enhance susceptibility to and/or severity of illness during national service.

Lunn and his colleagues³⁵² studied the pattern of respiratory illness in young children in Sheffield. They found that both upper and lower respiratory infections were related to the area in which the child lived, which in turn reflected pollution levels. FEV and FVC were also low in the most polluted areas.

More recently, Holland and his colleagues²²¹ studied some 10,000 school children in four areas in Kent. Peak expiratory flow rates were found to be related to residence, social class, family size, and past history of pneumonia, bronchitis, or asthma. These four factors appeared to act independently, but the effects were additive. The findings suggested that early environment can produce adverse changes that may persist and contribute to the subsequent development of chronic respiratory disease.

Colley and Holland³⁵³ attempted to assess the varying influences of smoking, area of residence, place of work, overcrowding, family size, social class, and genetic factors in the etiology of chronic respiratory symptoms and lung function in all members of families. A preliminary study of cough in 2342 families living in a

London suburb showed that in fathers exposed to both home and occupational hazards smoking and social class influenced the prevalence of cough but area of residence did not. In mothers, on the other hand, smoking and area of residence were important but social class was not. In the children, an effect of area of residence was also shown.

Colley and Reid²²³ have studied respiratory disease in over 10,000 children aged 6 to 10 years living in contrasting urban and rural areas of England and Wales. There was a pronounced social-class gradient in the frequency of chronic cough and history of bronchitis, and in the occurrence of diseases of the ears and nose as well. A consistent rise in the frequency of chest illnesses with increasing local levels of air pollution was seen only in children of semiskilled and unskilled workers. These trends paralleled similar trends in the frequency of killing and disabling bronchitis among adults in the same area. They were not explained by difference in domestic circumstances such as average number of persons per room, persons per dwelling, or rooms per dwelling.

Recently, Shy and his colleagues³⁵⁴⁻³⁵⁶ studied the effects of community exposures to nitrogen dioxide. Elementary school children living in four areas of Chattanooga, Tennessee, were selected. One area, in close proximity to a TNT plant, had high ambient levels of NO₂. The second area had relatively high levels of particulates. The third and fourth areas served as controls. Respiratory illness rates were consistently higher among all family segments in the high-NO₂-pollution area. The relative excess of respiratory illness among families exposed to high NO₂ compared with controls was 18.8 percent. The corresponding excess among families exposed to high particulates was 10.4 percent. Ventilatory lung function as measured by the 0.75-second forced expiratory volume (FEV_{0.75}) was also significantly lower in the high-NO₂ area compared with the controls. The differences in FEV, however, were neither as large nor as consistent as those between the high-NO₂ and the two control areas when these were considered separately. The biological implications of the statistically significant differences found when results from the control areas were pooled seem uncertain.

Yokohama and New Orleans Asthma Studies

In 1948, a respiratory condition was observed in American servicemen serving in the Yokohama-Tokyo area. Subsequently known as Yokohama asthma,³⁵⁷ the condition was characterized by a persistent, irritating cough and asthmatic attacks with coughing and wheezing. It was found to be more prevalent in cigarette smokers than in nonsmokers. Although it was first believed to be confined to American servicemen, it was subsequently found to occur in the Japanese. At autopsy, changes that resembled chronic bronchitis rather than asthma were noted. The condition is believed to result in part from industrial pollution in the Kanto Plain. The precise pollutants have not, however, been clearly identified.^{349,358-362}

Since 1958, epidemics of asthma have occurred in New Orleans that are recognized as such by sudden increases in the number of people seeking treatment at the emergency room of Charity Hospital. Characteristically, the epidemics occur in the first and third weeks of October, following the calendar rather than the weather. There is no day-of-the-week pattern; Saturdays and Sundays are as frequently involved as other days. Pollution described as "poor-combustion particles with associated silica" from burning dumps and dust from the New Orleans grain elevator have been suggested as possible causes, but neither suggestion is tenable. Increases

in asthma attacks may also be occurring concomitantly in other cities in Louisiana. The occurrence of a rather specific allergen in the city at certain times of the year has been postulated.³⁶³

Dose-response Relationships

Although some idea has been obtained of the levels of smoke and sulfur dioxide that may cause acute health effects (Table 19),^{91,113,190,291-294,300,303,312,340,350,364} it is important to realize that these two pollutants may not be the most important pollutants, but may only be indices of others that are more important. In London, excess mortality clearly resulted when 24-hour concentrations of smoke rose to 1000 $\mu\text{g}/\text{m}^3$ and concentrations of SO_2 rose to 750 $\mu\text{g}/\text{m}^3$. Levels of this magnitude may occur with average annual concentrations of 300 to 400 $\mu\text{g}/\text{m}^3$ smoke and 250 to 300 $\mu\text{g}/\text{m}^3$ SO_2 . No one can doubt that these concentrations are far too high and should not be allowed.

In London, 24-hour values of about 500 $\mu\text{g}/\text{m}^3$ smoke and 400 $\mu\text{g}/\text{m}^3$ SO_2 have led to exacerbations among bronchitis patients. Now that the average concentration of smoke in London is about 60 $\mu\text{g}/\text{m}^3$ and that of SO_2 is about 170 $\mu\text{g}/\text{m}^3$, it will be interesting to see if there is still some response among these susceptible patients to the highest levels that occur in the winter.

In the whole of Britain, correlations that appear to be linear can be shown for absenteeism resulting from bronchitis when winter smoke and SO_2 are 100 $\mu\text{g}/\text{m}^3$ and over. Furthermore, lower respiratory illnesses in children appear to be associated with average annual levels of smoke and SO_2 of 80 $\mu\text{g}/\text{m}^3$ and over.

In New York City, 24-hour averages of 5 coh (soiling index of particulates) and 2000 $\mu\text{g}/\text{m}^3$ SO_2 have resulted in mortality and 3 coh and 700 $\mu\text{g}/\text{m}^3$ SO_2 in morbidity. In Chicago, exacerbations of bronchitis have been associated with levels of SO_2 of about 750 $\mu\text{g}/\text{m}^3$. The particulate levels associated with the SO_2 pollution were not stated; however, the average annual value for Chicago for the appropriate years of the study, as reported by the National Air Surveillance Network, was 148 $\mu\text{g}/\text{m}^3$. In Buffalo, New York, there was a steady gradient in respiratory mortality corresponding to a pollutant gradient. The lowest levels were under 80 $\mu\text{g}/\text{m}^3$ particulates and sulfation of less than 0.45 mg/cm^2 -30 days.

Although these are rather inadequate data, it would perhaps be reasonable to conclude that average annual levels of particulates and of sulfur dioxide should both be under 100 $\mu\text{g}/\text{m}^3$.

Lambert and Reid¹¹³ have recently published the findings from a study that supports these conclusions. They carried out a survey by mail of respiratory symptoms in a representative sample of men and women living in England, Wales, and Scotland. Of the men and women believed to be aged 35 or over in the households sampled, 9975, thought to represent 74 percent of those aged 35 to 69 and able to respond, were analyzed. An increasing prevalence of persistent cough and phlegm and of chronic bronchitis with increasing age and with increasing cigarette consumption was confirmed. Chronic bronchitis was defined in this case as persistent cough and phlegm, breathlessness on walking, and a period of increased cough and phlegm lasting 3 weeks or more in the past 3 years. There was an excess in male nonsmokers as well as in smokers. Urban-rural gradients in this sample were not explained by smoking differences alone; the prevalence of symptoms

Table 19. PARTICULATE AND SULFUR DIOXIDE LEVELS AND EFFECTS ON HEALTH

Averaging time for pollution measurements	Place	Particulates		SO ₂		Effect	Author and year	Reference
		$\mu\text{g}/\text{m}^3$	cohs	$\mu\text{g}/\text{m}^3$	$\text{mg}/100 \text{ cm}^2 - 30 \text{ days}$			
24 hours	London	2000		1000		Mortality	Scott, 1959 Gore and Shaddick, 1958 Burgess and Shaddick, 1959	293 292 291
		1000		500		Mortality	Martin, 1964	364
		250		500		Exacerbations of bronchitis	Haller et al., 1969	303
		200		250		Increased absence from work	Angel et al., 1965	190
Winter	New York		6	1500		Mortality	McCarroll and Bradley, 1966	300
	Chicago	Not spec- ified		700		Exacerbations of bronchitis	Carnow et al., 1968	312
	Britain	200		200		Correlation of pollutants with bronchitis incidence	Ministry of Pensions and National Insur- ance, 1965	91
Annual	Britain	70		90		Lower respiratory in- fections in children	Douglas and Haller, 1966	350
	Britain	100		100		Bronchitis prevalence	Lambert and Reid, 1970	113
	Buffalo	100		--	0.30	Respiratory mortality	Winkelstein et al., 1967 and 1968	294, 340

increased with increasing air pollution independently of cigarette consumption. Local pollution appeared to have little effect in nonsmokers, but in smokers high levels of pollution were associated with more frequent respiratory symptoms. Prevalence of symptoms increased progressively from the lowest ($<100 \mu\text{g}/\text{m}^3$ smoke and SO_2 per year, on the average) to the highest ($\geq 200 \mu\text{g}/\text{m}^3$) pollutant levels. This study indicates, then, that pollution had a clear effect on respiratory symptoms, after age and cigarette smoking were taken into consideration. There was also an interaction between smoking and pollution.

Miscellaneous Studies

Various other epidemiological studies relative to air pollution have been carried out. Observations have, for example, been made on the mortality and morbidity of migrants in their country of adoption and have been compared with mortality and morbidity of the population of their country of origin and of the indigenous population in their country of adoption. The results suggest that a specific urban factor, possibly pollution, is playing a role. The importance of constitutional and environmental factors in the pathogenesis of chronic respiratory disease has been studied in Sweden using twin registry data.¹¹⁴ The authors found little evidence for a specific urban effect in Sweden, but concluded, rather, that air pollution there is of secondary importance to smoking in causing respiratory symptoms. Similar twin studies are being carried out in this country. Such studies would also be valuable in Britain, where the pollution levels are higher than in Sweden.

The effects of oxidant pollution on athletic performance were studied in Los Angeles and Seattle. In Los Angeles, the levels of oxidant and suspended particulates appeared to affect the times recorded; in Seattle they did not, possibly because the levels of the pollutants were lower.

Instead of relying on the somewhat unpredictable vagaries of nature to vary pollution levels, some investigators have carried out studies on patients by exposing them to polluted or filtered air in a specially designed room. In this way, Motley and Phelps³⁶⁵ showed subjective and objective improvement in patients with chronic obstructive lung disease who were supplied with pollutant-free air.

OCCUPATION

General Industrial Studies

Many irritants of the respiratory tract are encountered in industry. They range from relatively inert, insoluble dusts to fumes from the salts of rare metals, such as platinum, which can provoke dramatic sensitization manifested by asthma.³⁶⁶ They include substances such as cadmium and toluene di-isocyanate, which appear to have rather specific effects on the respiratory system. Gilson³⁶⁷ has classified the industrial pulmonary diseases as (1) mineral dust pneumoconioses, (2) vegetable dust pneumoconioses, and (3) pulmonary diseases caused by soluble gases and aerosols. This review is concerned less with these fairly specific occupational diseases than with the role of occupational exposures in the pathogenesis of chronic obstructive lung disease. Pneumoconiosis will be considered mainly in the light of its relationship to nonspecific chronic respiratory disease.

Dust exposure has been considered to be an important determinant of chronic respiratory disease at least since the time of Ramazzini (circa 1700). Nineteenth-

century clinicians stressed its importance, as the following rather characteristic passage indicates:

The diseases of the respiratory organs, so frequently caused by various arts and employments, especially... dry grinders and needle pointers; flax dressers and pearl and bone button makers; iron, brass, and metal filers; stone cutters, millstone makers, miners, and quarriers, particularly sandstone; wool carders and feather dressers, sawyers, turners, weavers, bakers, and starch makers. All these suffer more or less... from chronic bronchitis... persons thus occupied should be induced to preserve the beard on the upper lip, or the moustache, in order to intercept during respiration the mineral, vegetable or animal molecules diffused in the air surrounding them. 368

Greenhow,¹³ who probably knew more about industrial pulmonary diseases than any of his contemporaries (1860), never doubted the etiological importance of dust exposure. In this century, Collis,³⁶⁹ in his Milroy lecture of 1931, maintained that bronchitis was the first of the dust diseases, and Haldane believed that the disability from which British coal miners suffered in the first quarter of the 20th century was caused by bronchitis rather than by pneumoconiosis.

Mortality statistics support the view that occupation is a factor in chronic respiratory disease. Table 20 shows standardized mortality rates (SMRs) for pneumonia and bronchitis for certain occupational groups in the United Kingdom from 1949 through 1953.³⁷⁰ The table includes the socioeconomic class allocated to the various occupational groups. The low mortality ratios of men who worked in agriculture, forestry, and gardening were noted in both the 1931 and 1951 censuses.

Table 20. STANDARDIZED MORTALITY RATIOS
FOR BRONCHITIS IN MEN AGED 20 TO 64
AND THEIR WIVES IN ENGLAND AND WALES³⁷⁰

Occupation of men	Mortality ratios	
	Men	Wives
Miners	135	175
Hewers and getters	200	190
Others underground	93	177
Surface	131	139
Foundry workers	174	-
Moulders and core makers	194	217
Furnacemen	135	-
Laborers	159	-
Furnacemen	177	160
Openers, sorters, blenders, and carders	156	(500)

On the other hand, high ratios were observed on both occasions in hewers and getters of coal, furnacemen, moulders, masons, dock laborers, and general laborers. British coal miners have had consistently high death rates from bronchitis since 1900; however, their rates vary widely in different areas. ^{98, 369}

Information on occupational mortality in the United States is limited, but Guralnick ³⁷¹ and Enterline ³⁷² have published analyses of data from the 1950 U.S. census. Table 21, adapted from Guralnick ³⁷¹ and from U.S. Public Health Service data, ⁵⁸ presents standardized mortality ratios for diseases of the respiratory system for different occupations. The exceptionally high ratios for miners are striking. The magnitude of the difference between their ratios and those of other workers is quite different from that found in the United Kingdom, which to a large extent reflects the inclusion of pneumoconiosis in the American statistics. ³⁷² When such deaths are excluded, the ratios in the two countries become much more comparable.

Table 21. STANDARDIZED MORTALITY RATIOS GREATER THAN 150, BY OCCUPATION, FOR DISEASES OF THE RESPIRATORY SYSTEM EXCLUSIVE OF INFLUENZA AND PNEUMONIA IN UNITED STATES, 1950^a

Occupation	Standardized mortality ratio
Mine operatives and laborers (n.e.c.) ^b	933
Molders, metal	500
Laborers (n.e.c.), transportation equipment	433
Operatives and kindred workers, stone, clay, and glass products	250
Laborers (n.e.c.), primary metal industries	258
Taxicab drivers and chauffeurs	225
Laborers (n.e.c.), wholesale and retail trade	215
Operatives and kindred workers (n.e.c.), primary metal industries	195
Cooks, except private household	195
Laborers (n.e.c.), wholesale and retail trade	170
Laborers (n.e.c.), furniture; saw and planing mills; miscellaneous wood products	154
Lumbermen, raftsmen, and wood choppers	154
Operatives and kindred workers (n.e.c.), transportation, communication, and other public utilities	153

^aAdopted from Guralnick. ³⁷¹

^bNot elsewhere classified.

The interpretation of mortality statistics is difficult. Apart from diagnostic errors, it has been increasingly recognized that there may be serious biases between the occupational groups designated at the time of the census and those applicable at the time of death. ³⁷³ There is also a tendency for a man's widow, when registering his death, to promote him. Thus, a coal miner will often be recorded by his next of kin as having been a collier, whereas he would be correctly classified

(and usually he will have reported himself as such at the census) as a worker underground but not on the coal face. The problems of differentiating between the effects of occupational exposures and those of socioeconomic circumstances associated with the occupation--for example, family income, education, housing, childhood infections, and quality of medical care--are great. Attempts have been made to separate these factors by studying the mortality ratios of the wives of men in different occupations. The findings of such studies indicate that the wives of men who work in occupations with high SMRs for bronchitis also tend to have high ratios. This has been interpreted as indicating social rather than occupational factors in the genesis of bronchitis. Recently, Lowe³⁷⁴ questioned the validity of this interpretation on the grounds that the mortality rates of women are only a fraction of those of their husbands. It is not clear, however, why a lower absolute mortality rate among women should make the interpretation invalid. The relative trends in mortality with social class are roughly the same in men and women and this trend would appear to be more significant than the absolute levels of mortality.

A higher prevalence of respiratory symptoms in the wives of workers exposed to dust has been reported in several surveys.^{98,212,243} In Wales, the higher prevalence of symptoms was associated with a lower average FEV, but in Mullens, West Virginia, there was no difference in lung function between the wives of miners and the wives of nonminers. The full implications of the correlation in the prevalence of symptoms between husbands and wives is not clear at the moment. The finding is an interesting one, however, and deserves further study.

Morbidity by Occupation - Information on morbidity for the working population of Britain has been available since 1948 through the Ministry of Pensions and National Insurance. Periods of absenteeism resulting from bronchitis are high in miners and foundry workers but low in persons engaged in agriculture or forestry.⁴⁶ Absence rates are likely to be influenced by the heaviness of the job and also by whether or not any payment is made to a workman when he is sick. The heaviness of the job seems to play a role in the high respiratory disease rates among coal miners.³⁷⁵

From June 5, 1961, to June 2, 1962, a survey of sickness rates in a 5 percent sample of men and a 2.5 percent sample of women in the United Kingdom was carried out by the Ministry of Pensions and National Insurance.⁹¹ Certificates of incapacity for all illnesses that caused absence from work of 3 days or more were analyzed. The results for 620,000 men and 90,000 women were analyzed by occupation for 220 occupations and for 210 areas of residence. Table 22 shows the incidence (inception rates) and Table 23 shows days of incapacity for men aged 18 to 63 and for married and other women aged 18 to 58.⁹¹ The increasing inception rates for bronchitis with age in both men and women is clear; a smaller trend toward increase in inception with age is noted for pneumonia. The inception rates for bronchitis were, however, higher in women, particularly the married women, than in men. Days of incapacity follow the trends of the inception rates; they increase with age in men and women and are higher in women than in men. In view of the almost universal finding of a higher prevalence of chronic respiratory disease in men than in women, the higher frequency of attacks of bronchitis in women suggests that respiratory disease is more likely to be acute than chronic in women. This may be the result of a lesser exposure to respiratory irritants in women, or it could reflect more adequate management of an attack of bronchitis in them. One might recall the suggestion by Goodman and his colleagues⁸⁸ that one possible etiological factor in male chronic bronchitis is a too early return to work, particularly heavy and dusty work, after an attack of bronchitis.

Table 22. RESPIRATORY DISEASE INCEPTION RATES IN UNITED KINGDOM, 1961-1962 SURVEY⁹¹
(inception/100 sample population)

Disease	ISC ^a	Sex	Age, yr						
			All	<24	25-34	35-44	45-54	55-59	60-63
All causes		M	28	30	26	25	27	33	37
		F ₁ ^b	38	42	38	35	37	36 ^c	
		F ₂	34	38	30	27	29	29	
Asthma	241	M	0.2	0.2	0.2	0.1	0.2	0.2	0.2
		F ₁	0.2	0.2	0.2	0.4	0.2	0.1	
		F ₂	0.2	0.2	0.2	0.2	0.2	0.2	
Diseases of respiratory system	470-527	M	14	16	14	13	13	16	19
		F ₁	17	19	18	17	17	17	
		F ₂	19	22	16	13	13	13	
Acute upper respiratory infection	470-475	M	5	8	6	4	3	3	3
		F ₁	7	9	8	6	5	5	
		F ₂	9	12	7	5	4	4	
Influenza	480-483	M	6	7	6	6	5	5	6
		F ₁	7	7	7	6	6	6	
		F ₂	7	8	6	5	5	5	
Pneumonia	490-493	M	0.2	0.1	0.1	0.1	0.2	0.3	0.4
		F ₁	0.1	0.04	0.1	0.1	0.2	0.2	
		F ₂	0.1	0.1	0.1	0.1	0.2	0.3	
Bronchitis and emphysema (no mention of bronchitis)	500-502 527.1	M	4	2	2	3	5	8	10
		F ₁	4	3	3	5	5	7	
		F ₂	3	2	2	3	4	4	
Chronic sinusitis	513	M	0.4	0.5	0.5	0.5	0.3	0.2	0.2
		F ₁	0.6	0.6	0.7	0.8	0.4	0.4	
		F ₂	0.7	0.9	0.6	0.5	0.4	0.3	

^aInternational Statistical Code.

^bF₁ = married women; F₂ = other women.

^cAges 55-58.

Table 24 shows the age-standardized inception rates for bronchitis among various occupational groups.⁹¹ The high rates, approximately twice the average, for miners and quarrymen are well known, as are the low rates for workers in farming and forestry. Some of the differences between the occupational groups can be attributed to social class (Table 25), though within the social classes there appeared to be differences in incidence related to the heaviness of the job.⁹¹ Differences were also shown in this study among different geographic areas. Bronchitis rates were particularly high in South Wales and northwest and northeast England; but, though evidence for it is not given, the comment is made that a quarter to a third of the high inception rates among the miners could be attributed to the geographic

Table 23. INCAPACITY FOR WORK CAUSED BY RESPIRATORY DISEASE
IN UNITED KINGDOM, 1961-1962 SURVEY⁹¹
(days/100 sample population)

Disease	ISCa	Sex	Age, yr						
			All	24	25-34	35-44	45-54	55-59	60-63
All causes		M	885	552	584	711	984	1524	2163
		F1	1393	1253	1197	1347	1522	1906 ^c	
		F2	863	757	743	933	1188	1369	
Asthma	241	M	7	4	4	5	8	12	15
		F1	11	4	10	16	13	18	
		F2	7	4	5	10	11	14	
Respiratory diseases	470-527	M	285	183	187	209	307	513	756
		F1	340	286	281	365	386	453	
		F2	271	288	229	238	260	286	
Acute upper respiratory infection	470-475	M	52	70	59	48	40	41	43
		F1	90	108	96	85	78	67	
		F2	101	128	81	62	55	51	
Influenza	480-483	M	72	68	69	70	73	80	90
		F1	95	93	91	88	101	102	
		F2	81	86	80	68	72	80	
Pneumonia	490-493	M	7	3	3	6	9	16	20
		F1	5	1	3	6	11	6	
		F2	4	3	2	2	9	18	
Bronchitis	500-502	M	124	24	36	63	150	320	531
		F1	117	51	62	151	167	235	
		F2	55	38	41	85	101	112	
Sinusitis		M	6	5	7	7	5	4	4
		F1	10	9	12	13	8	7	
		F2	9	11	8	9	6	8	

^a International Statistical Code.

^b F1 = Married women; F2 = other women.

^c Ages 55-58.

distribution of the coal-mining regions. One fact that makes the interpretation of these high bronchitis rates among miners difficult is the observation made in this survey that the incidence of arthritis and rheumatism and, to a lesser extent, the incidence of psychosis and psychoneurosis also show rather similar gradations.

Field studies comparing different occupations - An early study of the prevalence of

Table 24. BRONCHITIS INCEPTION RATES IN MEN AGED 18-63
IN UNITED KINGDOM, 1961-1962 SURVEY⁹¹

Occupation	Bronchitis inception (standardized for age)	
	Rate, inception/100 men	Ratio, RSO/RAO ^a
All	3.69	100
Miners and quarrymen	7.24	196
Laborers (n.e.c.)	5.59	151
Operators of stationary engines, cranes, etc.	4.96	134
Furnace, forge, foundry, and rolling mill workers	4.71	128
Gas, coke, and chemicals makers	4.48	121
Warehousemen, storekeepers, packers, bottlers	4.17	113
Glass and ceramics makers	4.13	112
Transport and communications workers	4.11	111
Construction workers	4.10	111
Engineering and allied trades workers (n.e.c.)	3.80	103
Service, sport, and recreation workers	3.79	103
Painters and decorators	3.78	102
Makers of other products	3.56	96
Textile workers	3.53	96
Food, drink, and tobacco workers	3.46	94
Electrical and electronic workers	3.43	93
Woodworkers	3.27	89
Leather workers	3.17	86
Paper and printing workers	2.87	78
Clerical workers	2.67	72
Clothing workers	2.42	66
Farmers, foresters, and fishermen	2.25	61
Sales workers	2.11	57
Professional, technical workers, artists	1.89	51
Administrators and managers	1.08	29

^aRatio of rate for specific occupation (RSO) to rate for all occupations (RAO); for example, rate for miners and quarrymen, 7.24, divided by rate for all occupations, 3.69, is 196.

symptoms of chronic bronchitis was carried out by Clifton in an industrial firm in Sheffield in 1951.²⁴² She found that heavy cigarette smoking, past work in dusty jobs, and a family history of bronchitis were important factors. Since then many studies have been conducted that compare different occupational groups. Table 26 shows a number of population surveys of bronchitis and ventilatory capacity in men

Table 25. BRONCHITIS INCEPTION RATES AND INCAPACITY FOR WORK
CAUSED BY BRONCHITIS IN MEN AGED 18-63 IN UNITED KINGDOM,
1961-1962 SURVEY⁹¹

Occupational category	Rates, inception/1000 men (standardized for age)	Incapacity, days/1000 men
All categories	36.9	1235
Professional and Intermediate (I and II)	15.4	354
Skilled (nonagricultural) (III)	35.1	1040
Heavy	50.0	1442
Medium	35.9	1106
Light	25.8	679
Partly skilled (IV)	47.7	1573
Agricultural	19.3	506
Nonagricultural		
Heavy	60.1	2196
Medium	47.1	1540
Light	38.9	1429
Unskilled (nonagricultural) (V)		2306
Heavy	57.1	2364
Medium	50.1	1732

who work in dusty occupations that have been carried out in a manner comparable to the study by Clifton.^{98,111,214,235,243,376-378} The ratio of the percentage of bronchitis among the dust-exposed compared to that among the unexposed varies from about 1 to 1 to 3 to 1, with an exceptionally high ratio of 5 to 1 among fluor-spar workers in Canada. At the same time, the average ventilatory capacity (FEV_{1.0}) was consistently lower among the dust-exposed groups.

Specific Occupational Studies

Coal Miners

Miners versus nonminers - As early as 1924, Shurman³⁷⁹ found that the prevalence of bronchitis in underground workers was double that of mine office workers who had never been exposed to dust. Later, Bohme and Lent³⁸⁰ compared the frequency of bronchitis in hospital patients and found that the prevalence was 29.1 percent in miners compared with 15.5 percent in nonminers. More recent surveys have almost invariably indicated a higher prevalence of symptoms and of bronchitis in miners and ex-miners than in nonminers.^{98,195,212,214,243,381-386}

Enterline and Lainhart²¹² reported on surveys carried out in two coal mining areas, Mullens and Richwood, in West Virginia. Each community has a population of about 5000 inhabitants. Mullens, where mining began in 1912, is situated in east-central West Virginia, 100 miles east of Charleston. Mining has been carried

Table 26. POPULATION SURVEYS OF BRONCHITIS AND VENTILATORY CAPACITY IN MEN WORKING IN HIGH-DUST-EXPOSURE OCCUPATIONS

Country	Author and year	Refer- ence	Industry	Age	Sample population		Incidence of bronchitis, %			Ventilatory capacity		
					HDE ^a	Control	HDE	Control	Ratio, HDE/C	HDE	Control	Difference, HDE-C
England Leigh	Higgins <i>et al.</i> , 1956	214	Coal mining	55-64	132	84	23.5	10.7	2.2	2.17	2.39	-0.22
	Higgins <i>et al.</i> , 1959	98	Coal mining Foundry work	55-64 55-64	149 64	81 81	20.8 7.8	14.8 14.8	1.4 0.5	2.44 2.36	2.52 2.52	-0.12 -0.16
Wales Rhondda	Higgins <i>et al.</i> , 1961	243	Coal mining	35-64 ^b	275	262	28.5	9.2	3.1	2.53	2.87	-0.34
USA (West Virginia) Marion County	Higgins <i>et al.</i> , 1968	111	Coal mining	20-79 ^b	425	399	4.8	4.0	1.2	3.41	3.53	-0.12
	Enterline, 1967	376	Coal mining	21-64 ^b	225	224	na ^c 13.0 ^d	na ^d 6.5 ^d	na 2.0	3.01	3.18	-0.17
Richwood	Enterline, 1967	376	Coal mining	21-64 ^b	175	153	8.9	9.1	1.0	3.29	3.28	+0.01
	Parsons <i>et al.</i> , 1964	377	Fluorspar	20-70 ^b	301	56	21.3	4.0	5.3	2.86	3.09	-0.23
South Africa	Sluis-Cremer <i>et al.</i> , 1967	235	Gold mining	≥35 ^b	546	263	10.6	3.8	2.8	3.12	3.27	-0.15
	Pemberton <i>et al.</i> , 1968	378	Flax	≥35	262	594	12.6	5.6	2.3	na	na	na

^aHDE = high dust exposure; C = control.

^bAge-adjusted to the total population in the study.

^cNot available.

^dCough and sputum for ≤ 3 months.

on in that community since 1940. Representative samples of miners and other workers aged 21 to 64, and their wives, were studied using standardized methods that included questionnaires and simple ventilatory lung function tests. In Mullens, miners had a higher prevalence than nonminers of respiratory symptoms, particularly cough, wheezing, and breathlessness; previous history of pneumonia and pleurisy; and lower mean ventilatory lung function. In Richwood, no difference was found between miners and nonminers in either symptoms or lung function. In Mullens, miners' wives also had a higher prevalence of symptoms and past chest illnesses, but in Richwood there were no differences between the wives of miners and the wives of other men.

Higgins and his colleagues¹¹¹ studied mining communities in Marion County in northern West Virginia, where they found a slightly higher prevalence of respiratory symptoms and lower ventilatory lung function only in miners aged 50 years and over. The findings in these two surveys suggest that any differences in respiratory symptom prevalence and lung function between miners and nonminers in these areas are small. The areas studied may not, however, be representative of all mining areas in the United States. For example, Hyatt and his colleagues²⁰⁵ reported a much higher prevalence of respiratory symptoms in a sample of miners selected from labor union records. This was associated with a high prevalence of pneumoconiosis. It is possible, therefore, that differences in dust dosage might have accounted for the differences in respiratory disease found. The FEV appeared, however, to be rather similar in this study to that found by Higgins and his colleagues,³⁸⁷ so that observer variation cannot be excluded as a contributing factor in the differences found in symptom prevalence.

That there may be regional differences in the amount of respiratory disease found in different areas is well recognized. Regional differences in Britain have been discussed by Cochrane and his colleagues.³⁸⁸ Differences in the prevalence of pneumoconiosis among different areas have been noted by Lieben and McBride,³⁸⁹ Lainhart,^{390,391} and by O'Shea and his colleagues.¹⁵⁰

Beckenkamp³⁹² has stressed the fact that choice of occupation may play an important role in determining the prevalence of disease in particular occupational groups. Mine entrants in Germany during the 1950's and 1960's, for example, tended to be shorter, lighter, and less physically fit and mentally able than men entering other occupations. In a study conducted in the Rhondda Fach (Wales), however, Higgins and his colleagues found no evidence to support the hypothesis that mine entrants at that time were physically less able than men taking up other jobs. They pointed out that such selection could have occurred in the past but that there was no way now of establishing that fact.

Miners with pneumoconiosis versus miners without - Conflicting results have been obtained for the prevalence of bronchitis in miners with and without pneumoconiosis. In the United Kingdom, Hart and Aslett³⁹³ found that among Welsh coal miners aged 40 to 64 years, the prevalence of chronic bronchitis increased with radiological category. Newell and Brown²¹³ concluded from a study of 5117 working coal miners in four collieries in County Durham that symptoms and disability, as measured by withdrawal from coal-face work to less strenuous employment, were not related to the radiographic category of pneumoconiosis. In Germany, Trautman³⁹⁴ found that in "silicosis" Stages I and II the prevalence of bronchitis was not especially high, but that in Stage III it might reach 60 percent. Beckman³⁹⁵ found a higher prevalence of bronchitis in those with "silicosis" than in those without,

while Zorn,³⁹⁶ and Worth and Dickmans³⁹⁷ noted an increase in prevalence of bronchitis with increase in grade of "silicosis." On the other hand, Bohme and Lent,³⁸⁰ studying a group of miners who were no longer capable of work, found a higher prevalence of bronchitis in those without "silicosis" than in those with Stages I and II. Reichel and his colleagues³⁹⁸ reviewed the German literature on obstructive bronchitis in miners and reported findings for 674 miners without pneumoconiosis, 645 miners with various categories of pneumoconiosis, and a comparative group of 946 workers in the steel industry. They found a higher prevalence of cough and sputum among the miners than among the steel workers. There was no consistent relationship between the prevalence of cough and sputum and the x-ray category of pneumoconiosis. A lower prevalence of cough and sputum was noted, for example, among those having pneumoconiosis of radiographic categories B and C than among those with pneumoconiosis of categories O to A. Persons exposed to mine dust had slightly increased lung volumes and slightly reduced arterial oxygen tensions regardless of x-ray category. Increased airflow resistance was found only in those with advanced pneumoconiosis. The authors concluded that the chronic obstructive bronchitis observed was not caused mainly by exposure to mine dust. It is clear that the findings may be influenced greatly by the choice of population. In a series of studies of representative samples of mining communities, for instance, Higgins and his colleagues^{98, 214, 243} found little difference in the prevalence of bronchitis or in the mean FEV_{0.75} between those with and those without simple pneumoconiosis.

A slightly higher prevalence of respiratory symptoms and lower ventilatory lung function in those with simple pneumoconiosis was noted by Ashford and his colleagues³⁹⁹ in their studies of 30,000 coal miners in Britain, and by Hyatt²⁰⁵ and Higgins¹¹¹ in the United States.

In a survey of some 3700 working and nonworking Appalachian coal miners, Lainhart and his colleagues³⁹¹ found that the prevalence of breathlessness and persistent cough and sputum was higher in those with pneumoconiosis than in those without. The difference in cough was confined to working miners and the difference in breathlessness was small--about twofold--but there was no standardization for age. The prevalence of these symptoms also increased with the duration of underground work. Ventilatory lung function, especially the FEV, appeared to be lower than expected in miners irrespective of their category of pneumoconiosis. The discrepancy between observed and predicted FEV values was slightly greater for those with x-ray changes in pneumoconiosis than for those without. There appeared to be a progressive decrease in lung function with increasing duration of underground work. This partly reflected age differences, but some decline persisted after these were allowed for. Brasseur⁴⁰⁰ concluded in a study that micronodular or nodular categories of simple pneumoconiosis are associated with a decrease in ventilatory function and that, from category 1 to category 3 pneumoconiosis, a rise in pulmonary arterial pressure is seen, but that these changes are insufficient to affect a man's working capacity.

It seems reasonable to conclude that any effect simple pneumoconiosis may have on either symptom or bronchitis prevalence or ventilatory lung function is small. This conclusion is supported to some extent by the study by Caplan and his colleagues,⁴⁰¹ who examined 100 chest radiographs of miners with no pneumoconiosis and of those with categories 1, 2, and 3 simple pneumoconiosis for radiological evidence of emphysema. There was no evidence that radiologically detectable emphysema was related to dust deposition in the lungs. Certain observations on miner

mortality also support these findings. Cochrane and his colleagues⁴⁰² studied the mortality of miners and ex-miners living in the Rhondda Fach during the 6-year period, 1950 to 1956. Miners there had a higher mortality from all causes, particularly from respiratory diseases, than nonminers. The highest mortality rates were found among miners with progressive massive fibrosis. The radiographic category of simple pneumoconiosis was not, however, related to mortality.

Relation of respiratory symptoms and lung function to duration of underground and coal-face work - A number of attempts have been made to relate the prevalence of respiratory symptoms, bronchitis, and ventilatory lung function to long-term dust exposure by comparing miners who spent different periods in either underground or coal-face work. The results have been conflicting, some having shown a reduction in lung function and an increase in symptoms with increasing duration of exposure, 205, 243, 381, 386, 391, 403, 404 but others having shown little or no such effect.²⁴⁸ It seems safe to conclude that the dose/response relationships between dust exposure, when this is assessed by lifetime exposure, and the prevalence of symptoms or level of lung function are inconsistent. There are many reasons why this could be true: (1) the numbers studied have usually been small and thus liable to random fluctuation; (2) the small numbers have precluded adequate standardization for smoking; (3) selection into and out of each exposure category may be occurring for respiratory reasons; and, above all, (4) those capable of working in dust for 20 years or more must be the healthier survivors of those who originally started to work in mining. Possibly more important than any of the findings, however, is the concept that respiratory symptoms should be determined by a lifelong duration of dust exposure rather than by present concentration. In analyses based on this principle, concentration differences in exposure are ignored; therefore this factor may not be appropriate. Although a relationship has been demonstrated between prevalence of cough and sputum and current number of cigarettes smoked, no correlation was attempted between these symptoms and duration of smoking.

Gold Miners - Sluis-Cremer and his colleagues²³⁵ studied gold miners living in a community in the Transvaal, Republic of South Africa. Miners were compared with nonminers in a study of 827 men aged 35 years and over who lived in Carltonville on the Witwatersrand. Chronic bronchitis was more prevalent in smoking miners than in smoking nonminers for every age category, but this difference was not found in nonsmokers. Chronic bronchitis was slightly more prevalent in those with silicosis than in those without, but the difference was small and statistically insignificant. The prevalence of bronchitis was related to duration of occupational exposure to dust. The greatest difference in prevalence appeared to be between those with less than 1 year of service, in whom bronchitis was less prevalent, and those with 1 year or more. This observation is similar to those made by Higgins and Cochrane²⁴³ in studies of coal miners in the Rhondda Fach in South Wales, and by Hyatt and his colleagues²⁰⁵ in West Virginia, United States. Together these observations might suggest that the influence of dust exposure is relatively acute, which would corroborate the observation by Newell and Browne²¹³ in 1955 that there might be a sudden increase in symptoms in coal miners within about 5 years of starting coal-face work.

In a further paper on ventilatory lung function in the same group of men, Sluis-Cremer and Sichel⁴⁰⁵ showed that there was no difference in FEV_{1.0} between those exposed and those not exposed to dust, though somewhat lower values were found in those with bronchitis compared with the others. In this respect,

their study would seem to differ from other studies in which the ventilatory capacity in British coal miners has been found to be lower than that in nonminers.

An important study designed to correlate clinical, radiological, and physiological findings in life with post-mortem findings in the lungs was recently reported by Ryder and his colleagues.⁴⁰⁶ Observations were made on 247 coal miners who died between July 1965 and May 1967 and who, at the time of death, lived in an area of East Glamorgan, South Wales. A control group matched for age and sex was drawn from 1000 necropsies performed from 1964 through 1966 at the Cardiff Royal Infirmary. All the miners had been examined by the pneumoconiosis panel and most of them were receiving compensation for disability from pneumoconiosis. Emphysema was found approximately three times as frequently among the miners as among the nonminers. It was slightly more severe in those men whose chest x-rays had been categorized B or C than in those with categories O through A, but there were inconsistencies within the individual age groups, particularly among men aged 60 to 69 (the largest group), in whom the mean emphysema count was slightly less in those of categories B and C than in the rest. Extensive emphysema was found somewhat more often in men whose x-rays showed simple punctiform pneumoconiosis than in those with micronodular or nodular opacities. The extent of the emphysema was closely related to ventilatory impairment as indicated by the 1-second FEV test. Ryder's survey indicates that in this group of men emphysema was more frequent in miners than in other men but that it was poorly related to the radiological category of pneumoconiosis. The study has been criticized on the grounds that the sample of miners studied was unlikely to be representative of all miners. Fletcher⁴⁰⁷ noted the lack in Ryder's study of any appreciable age gradient in emphysema and FEV levels. Gilson and Oldham⁴⁰⁸ pointed out that the relationship between age and radiological category of pneumoconiosis that Cochrane found in the Rhondda Fach was not seen in Ryder's study. These commentators also noted that in comparing emphysema counts from x-rays that showed punctiform pneumoconiosis with those that showed micronodular and nodular types insufficient attention had been paid to age.

Uranium Miners - Archer and his colleagues^{409,410} studied the prevalence of respiratory symptoms and lung function in relation to ionizing radiation in uranium miners. They found an increase in the prevalence of persistent cough, shortness of breath, emphysema, and pneumoconiosis with increasing duration of underground work. Their lung function results are difficult to interpret. After age and cigarette smoking were taken into consideration, ventilatory lung function was found to be lower than normal in those who had received a higher dose of radiation during their working lives; however, the FEV values were higher in those currently exposed to high radiation levels. The authors suggest that either selection of men with lower ventilatory lung function for jobs involving high radiation exposure or a possible beneficial effect of such exposures on bronchospasm could explain the findings. They conclude, however, that long-term exposure to radiation adds to the loss in ventilatory function produced by aging and smoking.

Other Metal Miners - In 14,076 currently employed metal miners in the United States, Flinn and his colleagues⁴¹¹ studied ventilatory function and prevalence of respiratory symptoms and chest illnesses in relation to age; duration of occupation; x-ray changes attributable to silicosis; and smoking habits. They found that breathlessness increased with age from below 5 percent in men under 35 years to 18.4 percent in those 55 years and over. Breathlessness was twice as prevalent in those with simple silicosis as in those without. It also tended to increase with

increasing duration of employment in the industry. The prevalence of bronchitis increased slightly with age and was somewhat greater in those with silicosis. The relationship to ventilatory lung function of age, smoking, and duration of employment at underground mining was studied. Aging was found to have the largest effect; thus, between the ages of 35 and 55 years there was a reduction of 23 percent in $FEV_{1.0}$. This compared with a reduction of 10 percent attributable to heavy smoking and 2 percent attributable to 20 years of underground mining. The authors concluded that complicated pneumoconiosis probably had almost as much effect on pulmonary function as 20 years of aging and that cigarette smoking was of considerable importance compared with silicosis, although the tables presented by the authors do not indicate how this conclusion was reached. Simple silicosis was shown to be associated with a reduction of 4 percent and complicated silicosis with a reduction of 10 percent of observed as opposed to predicted FEV . This reduction appears to be the same as that attributed to heavy smoking but only about half that attributed to aging.

Pyrites Miners - In 1969, Sartorelli and his colleagues⁴¹² compared respiratory symptoms and ventilatory lung function in 984 miners working in a pyrites mine in Tuscany, Italy, with symptoms and function in 345 control workers who lived in the same area but who were not exposed to dusts or irritant gases. Chronic bronchitis was defined as presence of persistent cough and sputum for 3 months in the year for 2 or more successive years; physical signs of bronchitis on chest examinations; or a reduction in $FEV_{1.0}$ of more than 15 percent in comparison with expected, predicted normal values. Clear effects from both smoking and occupation were shown. Among nonsmoking miners, the prevalence of bronchitis was 6.8, 17.8, and 23.2 percent at 18 to 35, 36 to 50, and 51 to 68 years, respectively, compared with 0.0, 3.3, and 5.5 percent for these age groups in nonsmoking controls. Among smokers of 1 to 15 cigarettes per day, the findings in miners were 13.0, 32.7, and 39.8 percent compared with 3.8, 11.7, and 25 percent in controls. Among the heavier smokers (15 cigarettes per day and over), the corresponding figures were 31.8, 38.6, and 57.5 percent for miners and 4.0, 20.5, and 44.4 percent for controls. There was no significant difference in this study between miners with simple pneumoconiosis and those without. The higher prevalence of bronchitis and lower lung function in the pyrites miners was attributed to dust, sulfur dioxide, and thermal gradients, especially before ventilation was improved and dustiness reduced in 1963 and 1964.

Foundry Workers - The situation is perhaps even less clear in foundry workers than in miners. Keatinge and his colleagues⁴¹³ compared foundry workers with wagon builders. They found a higher prevalence of bronchitis in the foundry workers (20.6 percent) than in the wagon builders (14.9 percent). The foundrymen, however, lost less time from work for this cause than the wagon builders. Some of the difference was probably attributable to smoking since a higher proportion of the foundrymen were smokers. These workers suggested that the excess bronchitis mortality observed in foundry workers and their wives was the result of the geographical distribution of foundries rather than of the work carried out in them. Higgins and his colleagues⁹⁸ studied foundry workers, as well as coal miners and other workers not exposed to dust or fumes, from a representative sample of the population of Staveley, Derbyshire, England. Men who had been employed in foundry work only did not differ in prevalence of respiratory symptoms or in $FEV_{0.75}$ from men who had never been exposed to dust, but foundry workers who had also worked in mining and other dusty jobs had more prevalent symptoms and a lower $FEV_{0.75}$ than the corresponding nonexposed workers. Insofar as mining is

associated with respiratory symptoms and reduced lung function, this might have been expected. Alternatively, those who move from job to job may be more liable to respiratory disease than those who are more stable, or those who move may do so because of their ill health.

In a further study of the same town, the original sample was followed up after 9 years. At the same time, a new sample similar to that originally seen, but stratified by age and occupation, was also studied.¹⁹¹ A higher mortality in foundry workers was noted over the 9 years, particularly in the foundry workers who had simple pneumoconiosis. The mean FEV of those followed up was slightly lower in the foundry workers than in the group not exposed to dust, but the decline in FEV over the years appeared to be no different in the two groups. Among the foundry workers, however, those with simple pneumoconiosis had a lower average FEV and a somewhat greater average annual decline than those without. In the new cross-sectional study, the foundry workers recorded a slightly higher prevalence of breathlessness, chest illness, and chronic bronchitis--defined as persistent sputum and at least one chest illness in the past 3 years--than non-dust-exposed workers, but a similar prevalence of persistent cough and sputum (Table 27). They also recorded slightly lower average lung function values.

The findings in these surveys may be compared with a study carried out by Lloyd-Davies.⁴¹⁴ In a sample of 1 to 40 foundries in Great Britain, he surveyed 1911 men aged 35 to 64 and succeeded in examining 93.0 percent of them. After differences in smoking habits were taken into account, the prevalence of bronchitis was shown to be slightly but significantly higher in foundrymen than in men of sim-

TABLE 27. RESPIRATORY SYMPTOMS AND VENTILATORY LUNG FUNCTION
BY OCCUPATION, IN MEN AGED 25-74 IN STAVELEY, ENGLAND, 1966^a, 191

Symptom	Occupations with no dust exposure n=159	Miners and ex-miners n=179	Foundry and ex-foundry workers n=97	Other n=443
Cough	32.8	45.2	32.7	42.9
Sputum	31.1	51.8	40.9	47.7
Cough and sputum	27.0	38.1	27.3	35.4
Wheezing (most of time)	5.9	18.1	5.9	12.3
Breathlessness				
Grade 2 and over	12.9	30.9	16.9	18.1
Grade 3 and over	1.5	13.9	5.7	7.4
Chest illness within past 3 years (Duration of $\geq$ 1 week)	5.8	23.6	15.4	20.3
Chronic bronchitis	2.7	17.4	14.1	14.3
Mean FEV, liters	2.84	2.56	2.69	2.67
Mean FVC, liters	4.15	4.01	4.13	4.11
Mean FEV, percent	67.9	62.4	64.6	64.2

^aAge-adjusted to the total population.

ilar age employed in factories. The regression of FEV on age showed a steeper decline in foundrymen than in other workers.

Steel Workers - In a survey of a group of 20,000 South Wales steel workers, Lowe and his colleagues⁴¹⁵ used standard survey procedures and carried out a comprehensive environmental study. Both dust and sulfur dioxide (SO₂) were present in the steel mills and the men were categorized into four groups according to whether they were exposed to: (1) high dust and high SO₂; (2) high dust and low SO₂; (3) low dust and high SO₂; or (4) low dust and low SO₂. No relationship was found between ventilatory capacity or respiratory symptoms and exposure to either dust or SO₂ in this study.

Other Furnace and Chemical Workers - Higgins and his colleagues⁹⁸ found a high prevalence of respiratory symptoms and low lung function in a number of other groups in their study in Staveley, England. Furnace workers and chemical workers have a high prevalence of symptoms and a low average FEV. Coke-oven workers did not appear to differ greatly from non-dust-exposed workers in their experience of respiratory symptoms, but they had a lower FEV. More detailed analyses of these groups suggested that, apart from the particular occupations mentioned, these men had also been exposed to dust in other jobs. To some extent, their respiratory condition may therefore be attributed to mixed exposures. In addition, the chemical workers tended to be heavy smokers and this must have contributed to their disease.

Doll and his colleagues,⁴¹⁶ in a study of all employees and pensioners of four London area gas boards, showed that degree of exposures in coke-carbonizing and other gas-producing plants is related to mortality from lung cancer and bronchitis. Death rates from bronchitis were 126 percent higher in the most highly exposed groups than in those not exposed.

Textile, Grain, and Vegetable-product Workers - Textile workers have long been known to suffer from a high prevalence of respiratory disease.^{417,418} While byssinosis, the specific occupational disease, is responsible for some of the symptoms in workers exposed to cotton, flax, and hemp,⁴¹⁹⁻⁴²² it seems clear that exposure to such dusts may also result in the production or exacerbation of respiratory symptoms characteristic of bronchitis.^{420,421,423-426} Exposure to cotton, flax, and hemp dust may result in a reduction in ventilatory function during the working day.^{424,427-430} Apparently this reduction does not occur in persons exposed to man-made fibers.^{431,432} The decline is greatest on Mondays, which is the first day of return to work after absence from the mill, and becomes progressively smaller during the week. While the decline is usually greater in those subjects who are diagnosed as having byssinosis, it may also occur in persons without symptoms. The daily changes in ventilatory function may eventually lead to permanent disability and low ventilatory lung function.

Some studies have been conducted of workers who were exposed to mixtures of vegetable dusts. For example, Smith and his colleagues⁴³³ observed that in both men and women the prevalence of persistent cough and phlegm was higher and ventilatory lung function was lower in those who worked amid higher concentrations of flax and hemp dust than in those exposed to lower concentrations.

Cough, dyspnea, wheezing, and "grain fever," which is characterized by malaise, chills, and fever that usually occur several hours after the employee leaves work, has been noted by Kleinfeld and his colleagues⁴³⁴ in grain handlers. A previous history of pneumonia, dermatitis, or peptic ulcer was commoner in these workers than in the general population. Age, duration of dust exposure, allergy, and smoking were predisposing factors. In a similar study of grain handlers, Skoulas and his colleagues⁴³⁵ also observed that these symptoms increased with age, duration of service, and increased smoking. They noted that barley dust appeared to be the most pathogenic grain handled and that pathogenicity of grain dusts decreased in the order oats > rye > wheat. A previous history of allergy was found in a high proportion of cases. A reduction in ventilatory capacity within half an hour of starting work was observed by Gandevia and Ritchie⁴³⁶ in men exposed to wheat dust; these researchers also demonstrated a similar though smaller decline in men exposed to phosphate dust. The decreases were greater, or more consistent, in men who had persistent cough and sputum or who had a "productive cough on request" than in other workers.

Allergic sensitivity to various dusts is well recognized. Asthma and dermatitis or rhinitis, for example, have been shown to result from exposure to various wood dusts.^{422,437-441} The allergic reactions that may occur as a result of inhalation of organic dusts have been summarized by Pepys.⁴⁴² Such reactions are characteristic of those seen in farmer's lung, baggassosis, and pituitary snuff taker's lung; and of those that occur among mushroom-compost and other workers, and among bird fanciers. Precipitating antibodies to the appropriate antigens are usually present in these cases. The main features of this group of respiratory diseases are summarized in Table 28, 276, 443-465.

Workers Exposed to Toluene Di-isocyanate - Exposure to toluene di-isocyanate (TDI) results in changes in ventilatory lung function during the course of a working day and over longer periods of time.^{468,469} In studying 34 workers exposed to TDI, Peters and his colleagues⁴⁶⁹ noted a decline of 0.16 liter $\times$ FEV_{1.0} during the day that did not return to the base line by the following day. Follow-up after 6 months showed that there was a high correlation between the total decline in FEV over this period, and the daily decline. The rate of decline over 6 months was much greater than would have been expected on the basis of other studies of samples of the general population. Subsequently, Peters and his colleagues⁴⁷⁰ reviewed this same group of workers after 18 months. They noted an increasing decline in FEV that was greater in workers with respiratory symptoms than in those without. The similarity of the changes occurring during the day upon exposure to TDI to those resulting from exposure to certain vegetable dusts suggests that elucidation of the mechanism of reduction of lung function in TDI exposure might shed light on the mechanism of decline in other conditions as well. It is also possible that there may be other substances that could affect the lungs in a way similar to TDI.

ALLERGIES

Reactivity to Common Allergens

Turner-Warwick has recently (1969) reviewed hypersensitivity mechanisms and discussed the characteristics of each type.⁴⁷¹ Reaginic hypersensitivity, which is more often important in asthma caused by external allergens than in other conditions, is described as having the following characteristics: (1) the reagin binds strongly and lastingly to cell surfaces; (2) the reagin is not precipitating, agglutinating, or complement-fixing; (3) the Prausnitz-Kustner reaction gives an immediate flare and wheal; and (4) IgE immunoglobulins are increased in about 60 percent

Table 28. EXTRINSIC ALLERGIC ALVEOLITIS

Alveolitis ^a	Source of antigen	Antigen of precipitins present	Author and year	Reference
Farmer's lung	Moldy hay	<u>Micropolyspora faeni</u>	Pepys and Jenkins, 1965	443
		<u>Thermoactinomyces vulgaris</u>	Kobayashi <i>et al.</i> , 1963	444
Bagassosis	Moldy bagasse	<u>T. vulgaris</u>	Emanuel <i>et al.</i> , 1964	445
			Salvaggio <i>et al.</i> , 1967	446
			Hearn and Holford-Stevens, 1968	447
			Hargreave, Pepys, and Holford-Stevens, 1968	448
Mushroom worker's lung	Mushroom compost	<u>M. faeni</u> and <u>T. vulgaris</u>	Sakula, 1967	449
Fog-fever in cattle	Moldy hay	<u>M. faeni</u>	Jenkins and Pepys, 1965	450
Suberosis	Moldy oak bark cork dust	Moldy cork dust	Avila and Villar, 1968	451
New Guinea lung	Moldy thatch dust	Thatch of huts	Blackburn and Green, 1966	452
Maple-bark pneumonitis	Moldy maple bark	<u>Cryptostroma (Coniosporium) corticale</u>	Emanuel <i>et al.</i> , 1966	453
Malt worker's lung	Moldy barley; malt dust	<u>Aspergillus clavatus</u>	Riddle and Grant, 1967	454
		<u>Aspergillus fumigatus</u>	Vallery-Radot and Giroud, 1928	455
			Filip and Barborik, 1966	456
Bird fancier's lung	Pigeon; budgerigar; parrot; hen droppings	Serum protein and droppings antigens	Reed <i>et al.</i> , 1965	457
			Hargreave <i>et al.</i> , 1966	458
			Fink <i>et al.</i> , 1967	459
			Stiehm <i>et al.</i> , 1967	460
Pituitary snuff taker's lung	Heterologous pituitary powder	Serum protein and pituitary antigens	Pepys <i>et al.</i> , 1966	461
			Mahon <i>et al.</i> , 1967	462
Wheat weevil disease	Infested wheat flour	<u>Sitophilus granarius</u>	Lunn, 1966;	464
			Lunn and Hughes, 1967	276
Sequoiosis	Moldy redwood sawdust	<u>Graphium</u> , <u>Aureobasidium pullulans</u> (<u>Pullularia</u>)	Cohen <i>et al.</i> , 1967	465

^a Probable similar diseases include (1) smallpox handler's lung, Morris-Evans and Foreman, 1963;⁴⁶⁶ and (2) paprika splitter's lung, Hunter, 1959.⁴⁶⁷

of the cases to a mean level about six times greater than normal. The measurement of IgE immunoglobulins is valuable in differentiating between allergic and nonallergic asthma in which skin tests are negative, since in the latter condition normal or low IgE values have been found. Nonreaginic hypersensitivity may cause asthma

that comes on 4 to 5 hours after exposure to antigen. Precipitating, heat-stable antibody, characteristic of Type III arthus reactions, can usually be demonstrated. A delayed response to skin testing or inhalation challenge usually takes place. Sometimes both immediate and delayed responses occur; this dual asthma response is usually associated with dual responses to skin or inhalation challenge.

Eosinophilia

Blood and tissue eosinophilia is found in both intrinsic and extrinsic types of asthma. Recent experimental work suggests that the marrow stimulus for the production of eosinophils is mediated by lymphocytes, but their role in the asthmatic reaction is as yet unknown.

The tendency to allergy may be indicated by positive skin tests to common allergens or by blood or tissue eosinophilia. In addition to these two manifestations, hyperreactivity of the bronchial tree is often considered to be further evidence of an allergic tendency. Van der Lende²⁴ studied the relation of respiratory symptoms to each of these indices of allergy in three communities in The Netherlands. The skin test was considered in his study to be positive if a positive reaction was obtained to at least one of four allergens. An allergy score based on both the number of positive skin tests and the degree of reaction was also used. Neither of these indices appeared to be related to age, sex, or the presence of respiratory symptoms. In the most polluted community, however, a considerably higher proportion of positive skin reactions was observed than in the other two communities.

In women studied, the mean number of eosinophils in the blood was higher in those with respiratory symptoms than in those without. In men, however, a similar difference was suggested in only one of the three communities, and even here the difference between those with symptoms and those without was small and statistically insignificant. When the population was classified according to the presence or absence of blood eosinophilia (defined as ≥ 276 eosinophils/mm³), respiratory symptoms were more prevalent in those with eosinophilia than in those without. The differences were larger for those who had wheezing and asthmatic attacks than for those with persistent cough, sputum, or breathlessness.

Bronchial Hyperreactivity

Van der Lende used histamine inhalation studies to assess hyperreactivity of the bronchial tree. A positive test was defined as a decrease of 10 percent or more in the FEV_{1.0} or FVC upon inhalation of a concentration of histamine solution of 32 µg/ml or less. Hyperreactivity was found to be more frequent in those with respiratory symptoms than in those without. The proportion of positive reactors increased with age both for those without as well as for those with symptoms, although the trend with age was less consistent for the former group.

These observations seem to indicate that allergy as indicated by standard skin tests plays a rather small role in most cases of chronic obstructive respiratory disease, a conclusion that has been reached by other workers.^{472,473} On the other hand, both eosinophilia and bronchial hyperreactivity appear to be associated with symptomatology. The time relations of the associations are as yet inadequately defined, although there are some indications that the symptoms follow the constitutional predisposition of the individual.^{474,475} Some researchers, however, have noted that the tendency to hyperreactivity is not highly correlated with the occurrence

of allergy.⁴⁷⁶⁻⁴⁷⁸ It seems clear, therefore, that more attention should be paid in future epidemiological studies to these aspects of respiratory disease.

SMOKING

The role of smoking in the pathogenesis of chronic respiratory disease has been reviewed so thoroughly in reports issued by the Surgeon General, U.S. Public Health Service, 27, 28, 479, 480 that any attempt at comprehensive coverage here is clearly unnecessary. Instead, a number of aspects of smoking and respiratory disease will be surveyed with a view to reaching some conclusions on what further research is needed.

Mortality Rates

The higher mortality rates for bronchitis and "other diseases of the respiratory system" in men compared with women have long been apparent in the vital statistics of the United States and of other countries. Occupational exposures and smoking, especially cigarette smoking, seem to be the two most likely explanations for these sex differences. Evidence accumulated in recent years indicates that smoking is the more important of the two factors. It should be noted, however, that male children in Britain have a higher mortality from bronchitis than female children. To the extent that this occurs before any significant smoking is indulged in, it indicates that other factors, possibly constitutional in character, must be involved. Relatively little attention has been paid to trends in the sex ratio of mortality during the past few decades. The studies of Crofton and Crofton²⁴⁰ have already been mentioned. Fletcher⁴⁸¹ has pointed out that the trends in the male/female mortality ratios for bronchitis since 1916 in England and Wales have been similar to the male/female mortality ratios for lung cancer. It is likely that both trends are the result of the same cause or similar causes. Arguing by analogy, the most likely cause is cigarette smoking. Similar studies would be useful in countries where there are adequate vital statistics, notably the United States.

Prospective studies of mortality in relation to smoking habits have indicated that smoking is an important factor in death from chronic respiratory disease. Seven prospective studies were combined in the Surgeon General's Report³⁴ to obtain mortality ratios for bronchitis and emphysema for smokers and nonsmokers. Cigarette smokers had a mortality ratio for these diseases that was 6.1 times that of nonsmokers. Within different studies, the ratios varied from 2.3 in men in nine states to 12.5 in British doctors (Table 29).²⁷

Subsequently, Kahn⁴⁸² published the results of an 8-1/2-year follow-up of mortality in United States veterans. The age-adjusted mortality ratios found in this study for various categories of respiratory disease according to smoking habits are shown in Table 30. The ratios increased most markedly for deaths certified as resulting from emphysema (527.1), but only a slight increase occurred in ratios for deaths attributed to bronchitis with or without emphysema (500 to 502). It is interesting that the converse situation was found in Canadian veterans;⁴⁸³ this finding suggests again that diagnostic practices in the United States and Canada differ.

In the 10-year follow-up of mortality in British doctors, a pattern of chronic bronchitis mortality similar to that of lung cancer was found.⁴⁸⁴ The gradient increased with increased smoking, was higher in cigarette smokers (particularly in inhalers), and declined in those who gave up smoking. The standardized death rates

Table 29. MORTALITY RATIOS FOR BRONCHITIS (502)
AND EMPHYSEMA (527.1), BY SMOKING HABIT,
IN SEVEN PROSPECTIVE STUDIES^a

Study	Mortality ratios for cigarette smokers ^b
British doctors	12.5
Men in 9 states (U.S.)	2.3
United States Veterans	9.8
California occupational	4.3
California Legion	8.4
Canadian veterans	4.6
Men in 25 states (U.S.)	7.5
Total	6.1

^aDerived from Reference 27.

^bRatio for nonsmokers = 1.0.

for bronchitis, including emphysema (502, 527.1), and mortality ratios at the end of 10 years of observation in the study of British physicians are shown in Table 31 for comparison. The ratios are remarkably similar to those for United States veterans.

Hammond⁶⁷ determined the mortality rates for bronchitis and emphysema in women according to their smoking habits on the basis of a sample of 1 million men and women in the United States. The ratios for cigarette smokers are somewhat lower in women than in men in this study.

Morbidity Rates

Many studies of hospital and clinic patients, 118,241,256,485-490 of working groups, 80,90,106,201,210,219,244,491,492 representative samples of the community, 24,98,199,205,214,215,243,493 total communities, 206,224,494-496 and miscellaneous groups⁴⁹⁷ have shown that smoking is an important factor in the prevalence of respiratory disease. In many of these studies, standardized methods have been used and the relationship of smoking to various symptoms, as well as the relationship of certain clearly defined indices of bronchitis, have been presented.

These studies, many of which are admirably reviewed in the Surgeon General's Report,²⁷ should perhaps be summarized briefly. In both men and women the prevalence of cough and sputum is higher in smokers than in nonsmokers and increases with the amount smoked. The findings are much less consistent for other respiratory symptoms. Wheezing in the chest often shows a trend which is similar, though much less marked, to that seen for cough and sputum. The similarity may exist in part because some of the wheezing reported is caused by sputum in the respiratory tract. Chest illnesses during the past 3 years, breathlessness, bouts of coughing lasting 2 weeks or more--standard symptoms questioned in surveys--though usually more prevalent in smokers than in nonsmokers, have often been

Table 30. MORTALITY RATIOS FOR RESPIRATORY DISEASES, BY SMOKING HABITS,
IN UNITED STATES VETERANS^a

Disease	ISCB	Nonsmokers	Current cigarette consumption, cigarettes/day				Ex-smokers	Pipe and/or cigar only
			1-9	10-20	21-39	≥40	Total	
Bronchitis	(500-502)	1.0	2.13	4.34	4.01	6.91	2.86	0.48
Emphysema	(527.1)	1.0	5.58	11.94	16.27	20.86	9.09	1.34
Other respiratory diseases	(470-475, 510-526, 527.1)	1.0	1.36	1.25	1.57	2.50	1.22	0.69

^a Adopted from Kahn.⁴⁸²

^b International Statistical Code.

Table 31. STANDARDIZED DEATH RATES AND MORTALITY RATIOS,
BY SMOKING HABITS, FOR CHRONIC BRONCHITIS IN BRITISH DOCTORS

Smoking habits	Chronic bronchitis (n = 111)		Chronic bronchitis in association with cardiovascular disease (n = 55)	
	Rate, deaths/1000	Ratio	Rate, deaths/1000	Ratio
All men	0.34	6.8	0.17	5.7
Nonsmokers	0.05	1.0	0.03	1.0
Cigarette smokers				
1-14/day	0.34	6.8	0.15	5.0
15-24/day	0.64	12.8	0.20	6.7
25 and over	1.06	21.2	0.30	10.0
All amounts	0.58	11.6	0.21	7.0
Ex-cigarette smokers	0.38	7.6	0.16	5.3
Mixed smokers	0.33	6.6	0.21	7.0
Pipe and cigar smokers	0.15	3.0	0.12	4.0

^aAdapted from Doll and Hill.⁴⁸⁴

found to be inconsistently related to the quantity of tobacco smoked. An explanation that has been offered and that seems plausible is that smokers are likely to reduce their smoking when they develop breathlessness or chest illnesses that are more disabling than a mere "smoker's cough." This selection out of the category of less fit heavy smokers into the lighter smoking group could account for the inconsistent findings. Such an explanation needs to be tested, however, and to date there have been few attempts to measure this and various other forms of selection that are believed to occur.

Lung Function Tests

The vast majority of epidemiological results refer to some measurement of the ventilatory capacity, the most widely used of which has been the measurement of forced expiratory volume.^{81, 98, 109, 199, 200, 202, 206, 207, 224, 255, 262, 367, 498-501}

A considerable number of surveys, however, have used the peak expiratory flow, usually measured with the Wright peak flow meter.^{81, 137, 215, 218, 224, 228, 235, 236, 502} Other measurements of ventilatory capacity, such as the mid-maximal expiratory flow,⁵⁰³ flow rates at certain specified lung volumes,^{496, 499} and airways resistance¹³⁶ have sometimes been used in epidemiological studies. Other tests of lung function--nitrogen mixing,⁸¹ lung volumes,⁵⁰⁴ and diffusing capacity¹⁶¹--have been used only rarely.

The findings could be summarized by saying that lung function is consistently worse in smokers than in nonsmokers. Forced expiratory volume has almost invariably been found to be lower in smokers than in nonsmokers, and also usually lower than in ex-smokers; so, too, have peak expiratory flow rates, midmaximal expiratory flow rates, and flow rates at certain specified lung volumes. Vital

capacity is usually lower in smokers than in nonsmokers but the difference in vital capacity between the two groups is often less than the difference in FEV. Consequently, the ratio, FEV/FVC, may be the most discriminating simple index of lung function. Residual volume and residual volume as a percentage of total lung volume is higher in smokers than in nonsmokers. Mean lung function values within categories of smokers classified by number of cigarettes smoked are sometimes inconsistent. Thus, as in the case of the prevalence of symptoms, there is often little difference in lung function between light and heavy smokers. This is an unexpected finding, for which selection is the explanation most often advanced. The expected findings are those reported from studies of college students, in which differences in morbidity and lung function between smokers and nonsmokers were demonstrated after relatively short periods of exposure to cigarette smoke.^{496,499}

Epidemiological studies^{96,206} have shown that the FEV is lower in persons with respiratory symptoms than in those without. Lower values have been found in those with persistent cough and sputum or sputum alone. In view of the marked association of smoking with cough and sputum, the lower lung function values in smokers might be the result of cough and sputum, but some studies have shown that cigarette smoking, even in the absence of symptoms, is associated with a diminution of approximately 5 percent in such functions as the FEV or peak flow rate.^{201,358,500}

A few researchers have examined the trends over time in ventilatory lung function by conducting follow-up studies of groups after varying time periods.^{107,191,192,505,506} These studies have shown that decline in FEV is related to smoking habits. In the follow-up after 9 years of a sample of the population of an industrial town,¹⁹¹ Higgins and his colleagues showed that the rate of decline in FEV_{0.75} was higher in cigarette smokers than in nonsmokers or ex-smokers. The rate of decline was also higher in heavier than in lighter smokers.

Decline in ventilatory function with smoking has also been shown to be partly dependent on hypersecretion.^{107,505} Gregg, for example, found that in asymptomatic smokers there was no correlation between consumption and duration of smoking and impairment of peak expiratory flow (PEF).⁵⁰⁵ In smokers with hypersecretion, however, impairment of PEF was found increasingly in heavy smokers and in older smokers. It appears, therefore, that the impairment of PEF produced by smoking is caused at least partly by mucous hypersecretion. Fletcher and his colleagues¹⁰⁷ pointed out the difficulty of separating the effects of sputum volume and of smoking on decline in FEV, since, to a great extent, sputum production is dependent on smoking. In their study, they were unable to detect any additional effect of sputum volume over and above the effect of smoking on the decline in FEV. It is not clear, however, whether the effect they attributed to smoking was mediated through sputum production in the way Gregg suggests.⁵⁰⁵ Carey and his colleagues⁵⁰⁷ studied daily changes in ventilatory capacity and related these to smoking habits. In a group of public health inspectors in Belfast, Ireland, they found that the average morning and afternoon FEV_{1.0} was lower in smokers than in nonsmokers. The diurnal decline in FEV also tended to be greater in smokers than in nonsmokers.

Effects of Cessation of Smoking

The benefit of giving up smoking has long been noted by physicians.^{486,500} The effect of stopping smoking on subsequent mortality from bronchitis and emphysema has been shown in several prospective studies.^{482,484,509} Kahn, for

example, has noted that the age-specific probabilities of death for ex-smokers are lower than those for smokers when standardized for number of cigarettes smoked.⁴⁸² Doll and Hill found that the mortality ratios for those who gave up smoking first rose and then fell below the level for all smokers.⁴⁸⁴ In the 9-year follow-up of an English industrial population, the mortality of ex-smokers aged 55 to 64 was similar to that found in nonsmokers and was approximately half that of smokers.¹⁹¹ Clinicians have long advocated giving up smoking in cases of chronic respiratory disease. Systematic observations of the changes that occur after people quit smoking have, however, been relatively infrequent.

In an experimental clinic designed to help patients who have early symptoms of chronic bronchitis give up smoking, Wood and Meadows⁵¹⁰ noted that cough and sputum production were reduced in those who gave up smoking.

Campbell and Elder⁵¹¹ compared chronic bronchitics who continued to smoke with chronic bronchitics who no longer smoked. Apart from the smoking habit, the two groups were similar. Smokers had more exacerbations, lost more time from work, and were bedridden more than ex-smokers. They also had more visits to their medical practitioners and reported less favorably on the progress of their general condition, the nature of their cough, and the amount of sputum produced. In another group of 18 patients with chronic productive cough who had not smoked for several years, 10 reported that sputum production had ceased and 3 more reported that it had been considerably reduced.

Mitchell and his colleagues^{512,513} advised their patients to give up smoking and 42 percent did. Two-thirds of those who stopped experienced a striking relief from coughing. Mortality rates in these patients during the 20 years after the onset of their dyspnea was lower than that of the patients who continued to smoke. On the other hand, Burrows and Earle⁵¹⁴ were unable to show a reduction in mortality rate among patients who stopped smoking even when differences in FEV were allowed for.

Wynder and his colleagues⁵¹⁵ followed up a group of 224 ex-cigarette smokers. They noted that more than three-fourths of the group experienced one or more withdrawal symptoms, particularly an urge to have something in the mouth, irritability, inability to concentrate, and disorientation. Persistent cough was the symptom that showed the greatest improvement, ceasing in 77 percent of the subjects and improving in 17 percent. Throat-clearing ceased in about half the subjects. Weight gain occurred in 68 percent. These authors urged that further epidemiological studies of changes long believed to occur in ex-smokers be carried out.

In the 9-year follow-up study conducted by Higgins and his colleagues,¹⁹¹ a lower incidence of symptoms in those who originally had no symptoms and a higher remission of symptoms in those who originally had symptoms was noted in ex-smokers in comparison with current cigarette smokers.

INFECTIONS AND THERAPY

Bacterial (Bronchial)

The bronchi are sterile,⁵¹⁶⁻⁵²⁰ but sputum may often be contaminated by organisms from the pharynx. In chronic bronchitis, a variety of organisms can be isolated from the sputum and also from the bronchi at bronchoscopy, the two most

important of which are Haemophilus influenzae and Diplococcus pneumoniae.⁵²¹⁻⁵³⁴ The proportions in which they are found depend upon the group of patients being studied; the degree of purulence of the sputum, though this has been found in one study to be less important than is often thought;⁵²⁵ and the methods used to identify them, in particular, whether sputum examinations are performed once or repeatedly. The results in single sputum samples are affected by the inhomogeneity of the sputum.⁵²² During exacerbations of the disease, the flora of the bronchial tree appears to undergo a quantitative rather than a qualitative change. For example, Cooper and his colleagues⁵²⁶ noted a high or increased count of Haemophilus influenzae either alone or in conjunction with pneumococci in 40 out of 48 sputum specimens collected during acute exacerbations. Of 48 exacerbations, 21 were associated with high or increased counts of pneumococci either alone or in conjunction with H. influenzae. The importance of H. influenzae in chronic bronchitis was first suggested by Wilder in 1938. Additional support for the association is provided by serological demonstration of antibodies using tanned-red-cell antigens,⁵²⁷ complement fixation,⁵²⁸ and agglutinin and precipitin techniques.⁵²⁹⁻⁵³¹ While high antibody titres may be demonstrated in cases of chronic bronchitis, these appear to have little relation to the duration or severity of the disease or to the presence of an exacerbation.⁵²⁷ The results therefore support the view that H. influenzae colonizes the lower respiratory tract in chronic bronchitis but not that it causes the exacerbations.

Laurenzi *et al.*⁵¹⁸ and Green and Kass⁵³² have shown that in experimental animals inhaled bacteria are rapidly removed from the lungs. Hypoxia, alcohol, cold, and tobacco smoke interfere with this mechanism. Kass and his colleagues⁵³³ have also shown that, in mice, influenza virus interferes with the clearance of inhaled staphylococci. It is possible, therefore, that in chronic bronchitis the presence of bacteria in the lower respiratory tract indicates a failure to clear organisms that normally are inhaled but cleared by the lungs.

Viral and Mycoplasmal

The importance of viral infection in the pathogenesis of chronic bronchitis has been considered by a number of workers. Stuart-Harris *et al.*⁵²⁴ noted that fatal illnesses in patients with bronchitis increased during influenza epidemics. They also showed that influenza virus could be recovered from bronchitis patients during exacerbations. Subsequently, many other viruses have been associated with exacerbations; for example, respiratory syncytial virus;^{534, 535} parainfluenza and influenza viruses;⁵³⁶⁻⁵³⁸ and rhinoviruses.^{539, 540} Nonetheless, the role of viruses in chronic bronchitis is still uncertain. Fisher and colleagues⁵⁴¹ studied exacerbations of bronchitis in male bronchitics in Edinburgh, Scotland. They were able to show a significant increase in bacterial (pneumococci and H. influenzae), viral, and mycoplasmal pathogens during exacerbations compared with quiescent periods. Infective agents, though, were isolated in less than half the exacerbations and these workers concluded that viral and mycoplasmal infections did not appear to play a large part in exacerbations of chronic bronchitis. They did suggest, however, that this observation might reflect the limitations of methods currently available and that closer associations between viruses and chronic bronchitis might be found if newer techniques such as tissue culture⁵⁴² were used.

Attempts to assess the importance of various infections in the pathogenesis of respiratory disease have sometimes been made retrospectively. Thus Oswald *et al.*²⁵⁶ compared the frequency of colds in bronchitis patients and controls. They

found that the mean annual number of colds reported by the bronchitis patients was higher than that reported by the controls. Furthermore, whereas 27 percent of the colds in the controls "went down on the chest," 90 percent of the colds of the bronchitis patients did so.

In a study of a rural population, Higgins²¹⁵ observed that the average annual number of colds reported in the whole sample was two for both men and women and that 32 percent of these "went down on the chest" in men compared with 35 percent in women. Those with "chronic bronchitis," however, reported more colds--3 per annum in the men and 2.7 per annum in the women; 62 percent "went down on the chest" in the men and 88 percent in the women. In the same study, a higher frequency of previous pneumonia or bronchitis was reported by persons with persistent cough and sputum or "chronic bronchitis."

Because respiratory infections early in life are a possible cause of chronic disabling respiratory disease later, Reid³²⁵ has stressed that infections in childhood are an important aspect of the natural history of this disease. Reid and his colleagues have also shown that many of the international differences in mortality are apparent in the young.⁸³ It is likely that the increasing interest in conducting studies in young people^{221,543} will lead to advances in our understanding of the pathogenesis of respiratory disease.

Observations on the influence of exacerbations on the course of chronic respiratory disease during its early stages have been few. Angel's study showed that when exacerbations occurred any concomitant fall in ventilatory function was transitory.¹⁹⁰ Thus it appears that if bronchial infection causes chronic obstructive bronchitis it must do so gradually and not by any sudden, dramatic decline. No relationship was detected in this study between the degree of purulence of the sputum and the level or rate of decline in lung function. This suggests that infection cannot have played a major role in the course of the disease. In an attempt to identify causes of sputum production other than smoking, Fletcher⁴⁸¹ compared smokers and nonsmokers of similar age who produced similar amounts of sputum. Childhood bronchitis was significantly more common and asthma and discharging ears were somewhat more frequent among the nonsmokers. Fletcher concluded that childhood respiratory tract infections might initiate persistent hypersecretion in some subjects, who may in turn be less likely to take up cigarette smoking than their more fortunate fellows.

Chemotherapy

Many controlled trials of antibiotic drugs in chronic bronchitis have been carried out during the past 18 years.^{22,23} They have usually shown that penicillin or tetracycline given daily will reduce the duration of exacerbations of bronchitis and the number of days lost from work, but that they have no striking effect on the number of attacks of bronchitis or on the rate of decline in ventilatory lung function. The rate of decline of ventilatory lung function as measured by the FEV is greater in those with advanced disease. Most trials have been concerned with advanced cases of bronchitis, although the trial organized by the Medical Research Council's Working Party on Chemoprophylaxis and Chemotherapy in Early Chronic Bronchitis and those carried out by the British Tuberculosis Association^{544,545} are exceptions. The Medical Research Council trial, furthermore, lasted for 5 years. Four hundred ninety-seven men aged 40 to 59, with recurrent chest illness and with an FEV of 1.4 liters or over, were treated with oxytetracycline or placebos

continually from September to April. They initially were treated with 0.5 gram daily, but the dose was increased in the last 2 years of the trial to 1 gram and finally to 2 grams daily. Chloramphenicol (2 grams daily) or sulphamethoxypyridazine (0.5 gram daily) was given as treatment of exacerbations. Combinations of prophylactic and therapeutic regimes were allocated at random. Despite careful diagnostic standardization and selection, there was a wide variation in type of patients treated at the different clinics. Both the number and duration of exacerbations of bronchitis showed a large variation between clinics and a highly skewed distribution. This made it difficult to derive any simple index of the effect of either prophylaxis or treatment, and adjustment had to be made for interclinic variation. Oxytetracycline alone appeared to have no effect on the number of illnesses. In those patients who also received chloramphenicol, there was a significant reduction in the number who had many illnesses. Oxytetracycline appeared to reduce by one-third the total amount of time lost from work, but this estimate is uncertain because of a large range in the estimated values. Ventilatory capacity declined more rapidly in the patients than would have been expected for men of their age and smoking habits. Neither prophylaxis nor therapy had any effect on the rate of decline of FEV or on the volume or purulence of sputum. A similar conclusion has since been reached by other workers.^{546,547} This depressing and, at first sight, surprising finding might perhaps have been anticipated from the observation of Elmes and his colleagues⁵⁴⁸ that any improvement produced by Ampicillin therapy during exacerbations of bronchitis is only temporary; Cherniak and his colleagues⁵⁴⁹ however, noted in 1967 that repeated and protracted acute lower respiratory tract infections in patients with bronchiectasis leads to a greater decline in vital capacity and maximum breathing capacity than shorter and less frequent infections.

A number of studies have been reported on the effect of prednisolone therapy on chronic obstructive lung disease. Clifton and Stuart-Harris⁵⁵⁰ observed clinical improvement and increase in the FEV in about half of their patients, but the FEV returned to its previous level or below despite maintenance of steroid therapy. Long-term benefits from steroid therapy have been claimed by Ulmer and Nicolas.⁵⁵¹ In general, however, improvement from steroid therapy in patients with severe emphysema or obstructive airway disease has been slight or absent.^{552,553}

The effect of bronchodilators, either alone or in combination with wetting agents, was assessed by Wilson and Wilson, mainly in patients with advanced disease.⁵⁵⁴⁻⁵⁵⁷ It would appear unlikely that therapy would improve the course of the disease at that stage. It seems desirable, however, for these measures to be instituted at an earlier stage of the disease to see if they are effective. Controlled trials have been advocated by Jones and Fletcher.⁵⁵⁸ Various authors have emphasized the greater improvement produced by aerosols in asthmatic compared with bronchitic patients.^{559,560}

SOCIOECONOMIC STATUS

An inverse relationship between family income and mortality rates for pneumonia in white children under 1 year of age was shown in the U.S. National Health Survey in 1935 and 1936.⁵⁶¹ In the national growth and development study already described in the section on air pollution, Douglas⁵⁶² found that lower respiratory tract infections, as measured by episodes of bronchitis or pneumonia sufficiently severe to require treatment from a general practitioner or admission to hospital, were about four times as high in the first 6 months of life for infants of manual workers as for infants of other salaried or professional workers. Douglas

believed that this probably reflected the home conditions and pattern of living of the manual workers. He pointed out that from an early age the infants were taken on buses and trains and had contact with neighbors, friends, and relations, with a resultant increased frequency of early infections. The incidence of colds was found to be higher in the infants of the poor and more of their colds occurred at earlier ages.

Goodman and his colleagues⁸⁸ suggested that the fivefold social class mortality gradient might be caused by overcrowding, infection, malnutrition, and the inability to treat respiratory infections with enough care. Meadows⁹² also indicated that a downward drift in social class may occur in those who have chronic bronchitis.

All children born (1142) in May and June 1947 to women residents in Newcastle, England, were enrolled in a prospective study known as the 1000 Families Study.^{563,564} Bronchitis and pneumonia in the first year were significantly related to social class, overcrowding, and standards of maternal care. A tenfold increase was found in the mean number of attacks of severe respiratory disease among unskilled as opposed to professional families. Subsequently, in a survey in Newcastle of chronic bronchitis morbidity in persons over 30 years of age, Ogilvie and Newell¹⁷ found a significant association between morbidity and social class and morbidity and unemployment. This association was considered to be economic rather than occupational.

The California Health Survey¹⁹ also showed an increased prevalence of chronic bronchitis in those with a family income of less than \$2000 per annum, but a high proportion of those with incomes in this range were aged 65 years and over. Much of the apparent effect of low income on bronchitis prevalence in this survey appeared really to be a reflection of age.

An association between educational level and prevalence of respiratory symptoms and level of ventilatory lung function was noted by Enterline and Lainhart²¹² in their studies of mining communities in southern West Virginia. The association was subsequently supported by studies carried out in the northern part of the state.³⁸⁷ Some, but not all, of the association could be explained by differences in height or smoking habits, which also differed among the respective educational categories of the study population.

WEATHER AND CLIMATE

Weather and climate have long been believed to play a role in the pathogenesis of chronic respiratory disease. Most of the observations seem to have been made in the United Kingdom, presumably because of the important role the weather plays in daily life there. Farr⁵⁶⁴ observed in 1885 that the commonest causes of death during the cold months were pulmonary diseases and the cerebral diseases of the aged. Young later found that deaths from bronchitis and pneumonia in children were correlated with ambient temperature during the preceding week.⁵⁶⁶ In 1927, Woods noted that low temperature was correlated with pneumonia deaths in persons aged 5 to 40 but not in children under 5 years.⁵⁶⁷ The Payling-Wrights, however, observed similar correlations in young children.⁵⁶⁸ More recently, Boyd found that mortality from chronic respiratory disease in England and Wales was correlated with temperature and absolute humidity.⁵⁶⁹ Holland and his colleagues, using as their index the requests made for admission to hospitals through the Emergency

Bed Service in London from 1955 through 1958, showed that, allowing for seasonal effects, morbidity from respiratory diseases was related to temperature for persons aged 15 years and over.⁵⁷⁰

Cough prescriptions have been used by Loudon⁵⁷¹ as a measure of cough frequency. He correlated prescription frequency in two Dallas hospitals with nine meteorological measurements. By means of factor analysis he was able to show correlations between prescription frequency and temperature, hours of sunshine and humidity, and both relative and total precipitation.

McKerrow and Rossiter³⁸⁷ have drawn attention to cyclical changes in ventilatory capacity that take place during the year. In repeated measurements of the FEV in retired coal miners with pneumoconiosis who worked at a light engineering factory, they found that the FEV was lowest in the winter and highest in the summer months. The reason for this cyclical fluctuation in FEV is not known. Neither change in clothing nor environmental changes appeared responsible. The winter decline was not clearly related to respiratory infection inasmuch as it occurred in normal subjects who had no respiratory infections. These authors suggested that the cyclical changes were caused by a biological rhythm linked to environmental temperature. In this study, a greater deterioration in FEV with age was noted in subjects who had attacks of purulent sputum. Cyclical variation in airways resistance comparable to the variation in FEV has been reported by several authors.^{316,572,573}

Cassell and his colleagues⁵⁷⁴ pointed out the difficulties of assessing the influence on health of a number of related environmental factors, particularly when these are interrelated. These workers followed a panel of New York families, comprising 1747 persons, for 45 weeks. Weekly interviews were conducted and the information that was obtained was related to indices of air pollution and various meteorological measurements. They were able to show relations between weather, particularly cold weather and humidity, and frequency of cough, sore throat, and the common cold.

MISCELLANEOUS FACTORS

Poisonous Gas Exposure in World War I

There have been a few studies of the effects of gassing, in World War I, on respiratory diseases. Among residents of Staveley, Derbyshire, England, Higgins and his colleagues⁹⁸ noted an exceptionally high prevalence of chronic bronchitis in men aged 55 to 64 who said they had been gassed in the war. More recently, Wada and his colleagues⁵⁷⁵ studied the clinical and pathological manifestations of respiratory damage in retired workers who were exposed to poisonous gases while working in a poison gas factory. A high incidence of malignancy was noted and most diseases were superimposed on chronic bronchitis. Exposure to mustard gas appeared to be especially significant. Case and Lea⁵⁷⁶ in 1955, found a very high prevalence of chronic bronchitis in British World War I veterans who had been pensioned because of mustard gas poisoning. This, of course, could be explained by postulating that men who had been gassed and who also developed chronic bronchitis would be those most likely to apply for a pension. In a comparable investigation conducted by Beebe, however, this postulation does not seem to be a valid explanation for the high incidence of bronchitis found in American veterans who had been gassed.⁵⁷⁷ Reduced expiratory flow rates and a high rate of incidence of chronic

bronchitis have recently been demonstrated in former employees of a poison gas factory in Japan.⁵⁷⁸

Infection of Teeth and Sinuses

Joules included infection of the teeth and sinuses in his list of factors involved in chronic bronchitis.⁴⁸⁶ Corroborating Joules' premise, Summers and Oberman, in a study of oral disease in relation to 12 selected variables in Tecumseh, Michigan, found that periodontal disease was inversely related to FEV in both men and women.⁵⁷⁹ In men, an association between smoking and periodontal disease explained most of the relationship, but in women, after allowing for smoking, the FEV was still significantly related to periodontal disease. A few observations have been made on sinus infection, though perhaps fewer than might have been expected from the widespread use of such clinical terms as "sino-bronchitis." A major difficulty lies in the wide variability in interpretations of the kind of sinus x-rays that can be obtained in epidemiological surveys. In a study of men aged 55 to 64, there appeared to be little relationship between the condition of the sinuses and either chronic respiratory symptoms or lung function (Pneumoconiosis Research Unit, Medical Research Council, U.K.; unpublished observation). It is possible that a closer relationship between sinus infection contracted at an earlier age and subsequent chronic lung disease might be observed. Further work in this area might be profitable.

Postoperative Pulmonary Complications

Albert and his colleagues⁵⁸⁰ have drawn attention to the high frequency of pulmonary complications that have followed high laparotomy, especially when the operation was performed in an emergency. During 1960 and 1961, among 4784 operations performed in a department of general surgery, 60 patients (1.3 percent) developed postoperative pulmonary complications. In patients undergoing high laparotomy, pulmonary complications occurred in 5 percent, and when it was an emergency operation, the incidence was 12 percent. The long-term implications of this phenomenon for chronic respiratory disease are not known. It is an area that might repay further study.

FOLLOW-UP STUDIES OF CHRONIC RESPIRATORY DISEASE

A number of valuable clinical investigations have been made in which carefully studied groups of bronchitis patients have been observed over a number of years in order to determine the course and outcome of the disease. Platts and her colleagues found that ventilatory capacity, MBC, and residual air as percentage of total lung volume were of little prognostic value in patients with chronic bronchitis in Sheffield, England.⁵⁸¹ Mitchell and his colleagues⁵¹² followed 150 patients with chronic obstructive bronchopulmonary disease. They noted the risk of cardiac complications and the serious prognostic implications of alterations in the arterial blood gases. The use of lung function tests to assess prognosis was first used by Bates and his colleagues⁵⁸² in 59 patients with emphysema and bronchitis. Ventilatory capacity, functional residual capacity, and mixing efficiency of the lungs were found to be of little value in prognosis; however, DLCO underwent a progressive fall, especially before the onset of right ventricular failure. Boushy and Coates⁵⁸³ followed 83 patients with diffuse obstructive emphysema for 2 to 6 years, during which time 48 of them died. The degree of impairment of forced vital capacity (VC), the maximum voluntary ventilation (MVV), the height of PaCO_2 , and the level

of SaO_2 all correlated with the poorness of the prognosis. In a major study carried out by the Veterans' Administration in the U.S., a total of 487 patients, selected on the basis of a high residual lung capacity/total lung capacity ratio, were admitted into the study between 1958 and 1960.⁵⁸⁴ In the 4-1/2-year period of follow-up, 48 percent of the patients died, which was five and one-half times the mortality expected. Impairment of ventilatory function and gas exchange were significant prognostic indicators.

Oswald and his colleagues⁵⁸⁵ and Medvei and Oswald¹⁹¹ carried out a study of 212 civil servants attending the Brompton Hospital in London. They presented their findings after 5 and 10 years. Mortality in excess of normal was approximately fourfold, largely from respiratory or cardiac causes. The serious prognostic implication of generalized emphysema detected by the chest x-ray was noted.

Earle and Burrows⁵⁸⁶, and Burrows and Earle⁵¹⁴ published their findings in 200 patients who were enrolled in a special follow-up clinic at the University of Chicago Hospitals between 1960 and 1964. The mean age of these patients was 59 years and their mean $\text{FEV}_{1.0}$ was 1.02 liters, indicating a moderately severe level of impairment. Prognosis was related to the degree of airways obstruction as indicated by such ventilatory function tests as the $\text{FEV}_{1.0}$, VC, and MVV; to cor pulmonale and a group of factors such as resting heart rate, presence of peripheral edema, and ECG changes considered to be related to cor pulmonale; to bronchopulmonary infections indicated by recurrent winter illnesses, chronic or continuous sputum production, and ability to work; and to miscellaneous factors including physician assessment of dyspnea during a standard exercise test. Of these, the most valuable pulmonary function tests for assessing prognosis were those indicating airways obstruction.

Davies and McClement carried out a 10- to 13-1/2-year follow-up of 95 patients who were admitted to the Emphysema Clinic at Bellevue Hospital, New York, between April 1955 and July 1957.⁵⁸⁷ At 5 years, 58 percent of the patients had died, which was some four times the expected rate for men of similar age and the same race in the general community. The patients who survived the 5-year period had death rates that approximated those of the United States general population. The authors concluded that patients with less severe types of disease might have a normal life expectancy. The study confirmed the serious prognostic implications of chronic arterial oxygen unsaturation, chronic CO_2 retention, a persistently low MBC, or cor pulmonale.

Howard followed a group of 125 patients (112 male and 13 female) at 1- or 2-month intervals for a number of years.⁵⁰⁶ The FEV was measured each time the patient was seen. The regression of the change of FEV with time was calculated for the whole period of observation and the slope or regression coefficient was expressed in liters per year. The mean age of the patients was 60.7 years and the mean period of follow-up was 7.1 years. The mean initial FEV was 1.2 liters. Wide swings in the FEV were found in asthmatic patients. The rate of decline tended to remain constant for long periods, though temporary seasonal and spontaneous fluctuations were also noted. In 21 cases in which a decline in FEV occurred within 6 months that was greater than two standard deviations of the regression, an acute exacerbation could be implicated in 10. The patients in whom these sharp falls in FEV occurred were much heavier smokers than the other patients. Howard concluded that although clinically recognizable bacterial infection and frequent exacerbations might contribute to the decline in ventilatory function, they were not essential to it.

These clinical observations have been based on patients with advanced chronic respiratory disease. Few observations have been made on more representative groups of people.

Higgins and Oldham followed up, after 5 years, a random sample of miners and nonminers living in the Rhondda Fach in South Wales.¹⁹⁰ They found that the average rate of decline in FEV_{0.75} was 0.046 liter each year. Subsequently, in a 9-year follow-up of an industrial town population, Higgins and his colleagues found a decline of 0.03 liter per year in men aged 25 to 34 and 0.04 liter per year in men aged 55 to 64. The decline was inconsistently related to occupational exposure but was higher in smokers than in nonsmokers or ex-smokers.¹⁹¹ In these surveys, mortality was higher in those with many symptoms than in those without symptoms. The degree of breathlessness that was recorded on the first survey appeared to be the most useful symptomatic indication of prognosis. Mortality in men aged 55 to 69 was related particularly to FEV.³⁴

Wilhelmsen and his colleagues measured the ventilatory capacity in a group of 313 men (aged 50 years) in 1963 and again in 1967. They found that vital capacity, forced expiratory volume, and maximum expiratory flow all fell more in smokers than in nonsmokers or ex-smokers. Lesser declines were also observed in those who gave up smoking during the 5 years.⁵⁸⁸

Comstock and his colleagues followed up 670 male telephone company workers aged 40 to 59 years after 6 years. There was a greater decline in FEV_{1.0} and a greater increase in sputum volume among those who continued to smoke cigarettes, especially in the heavy smokers and those who used nonfilter cigarettes. The smallest decline in FEV occurred among those who gave up smoking cigarettes.⁵⁸⁹

Fletcher and his colleagues studied approximately 1250 working men aged 30 to 59 who were seen at 6-month intervals from 1961 to 1966.^{107,407} Standardized questions, FEV_{1.0}, and measurements of sputum volume and cytology were made. A mean decline in FEV of 0.026 liter per year was noted. The decline in FEV was related to level of FEV, a greater decline being observed for those with an initially low FEV. This decline was shown to be particularly related to the ratio between FEV and FVC. The decline in FEV was greater in cigarette smokers than in nonsmokers and was greater in heavier than in lighter smokers. Chest illnesses did not appear to influence the rate of decline of FEV, although chest illnesses were more frequent in those with a low FEV and, especially, in those with a low FEV to FVC ratio. Sputum volume, apart from cigarette smoking, did not appear to influence the rate of decline in FEV. Chest infections were much more frequent in those with sputum than in those without and tended to increase with increasing sputum volume. Mucous hypersecretion and low FEV/FVC appeared to increase the liability to chest illnesses independently.

In 1959 and 1960, in Tecumseh, Michigan, 5140 adults were classified on the basis of respiratory symptoms, respiratory disease, and ventilatory capacity.¹¹⁰ Mortality during the next 4 years was related to the initial observations. Chronic respiratory disease was an underlying or contributory cause in 4 percent of all deaths. Subjects with respiratory disease, or with decreased ventilatory lung function or respiratory symptoms had higher mortality rates than those without these conditions. Mortality among men and women with cough and sputum, shortness of breath, or low levels of FEV_{1.0} exceeded the number of deaths from coronary heart disease. Shortness of breath was the best single predictor of death, especially

of death from coronary heart disease. Cough and phlegm were not associated with increased mortality in the absence of shortness of breath. Among men, cigarette smokers suffered more deaths than nonsmokers of the same age, but the rates in smoking and nonsmoking women were similar.

The average annual decline in FEV in patients with respiratory disease is higher than the decline found in these population surveys. Thus, in the trial of chemotherapy in early bronchitis carried out by the British Medical Research Council, an average decline of 0.08 liter per year was found. Howard observed a similar average decline in hospital patients with bronchitis.⁵⁰⁶

RECOMMENDATIONS FOR FURTHER RESEARCH

ETIOLOGY OF RESPIRATORY DISEASE

Cigarette smoking is generally agreed to be the most important factor in the development and progression of respiratory disease, but why some people are affected by smoking and develop hypersecretion with cough and sputum while others are apparently more resistant or even remain unaffected is much less certain. Clearly, attempts to identify those individuals who are susceptible and to identify factors, such as infections, that could interact with tobacco smoke to initiate respiratory disease are urgently needed. The role of other suspected etiological factors either as initiators of disease or as aggravating influences on it once it has started is much less certain. These comments apply (1) to air pollution, in general, and, in particular, to air pollution in the United States, since so much of the research that has led to its indictment as a factor in respiratory disease has been conducted in other countries; (2) to exposure to occupational irritants, particularly to dusts, fumes, and gases; and (3) to infections, both bacterial and viral.

Longitudinal studies are needed of people who are exposed to varying degrees and types of pollution and to various occupational irritants--and who have suffered from various respiratory and other infections--to determine the role of these factors as initiators of chronic respiratory disease and, wherever possible, to establish dose/response relationships. Such studies would also shed light on the potential of these factors to exacerbate disease and influence its course. The study would have to be conducted on large groups of adults so that any findings can be standardized for different smoking habits. Recent studies indicate, however, that the seeds of chronic respiratory disease may be sown in childhood. Children are therefore particularly useful for evaluating the role of certain pollutants and irritants, as well as of other factors. Since smoking is rare until at least the age of 15 years, it is possible that deleterious effects can be demonstrated in smaller numbers of children than of adults. It is important that, whenever possible, observations be made before any potentially harmful exposures occur. In industry, pre-employment examinations should include at least the questions recommended in the short Medical Research Council Questionnaire and should include a competently performed test of FEV and FVC. If there is likelihood of pneumoconiosis, a base line chest radiograph should also be included.

Constitutional predisposition to respiratory disease has been studied, primarily by workers in The Netherlands and in Sweden. Increasingly, evidence points to constitutional differences that may influence susceptibility to respiratory disease. It is essential that this be studied adequately in representative samples of the community and not merely in hospital and clinic patients or in otherwise highly selected groups. Not only should population surveys for respiratory disease include tests for such conditions as alpha₁-antitrypsin deficiency and cystic disease, but they should also include measurements of (1) skin sensitivity to common allergens, (2) bronchial reactivity to histamine inhalation, and (3) sputum and blood eosinophilia. At present, it is difficult to ascertain whether these so-called indices of allergic tendency precede or follow the development of bronchial hypersecretion.

DIFFERENTIATION OF CHRONIC RESPIRATORY DISEASE

One cannot help being impressed by the crudity of the present classifications of respiratory conditions used in most surveys. Studies are needed, therefore, to develop indices by which to differentiate asthma and emphysema from chronic bronchitis. Recent evidence suggests that radiological differentiation of emphysema from chronic obstructive bronchial disease may be more feasible than has been thought. Further work is needed also to determine which tests are most suitable for field surveys.⁵⁹⁰

The differentiation of asthma will probably be accomplished best on the basis of tests of bronchial reactivity and evidence of skin sensitivity. Few surveys to date have included such tests. Inclusion of observations on immunoglobulins should also be considered.

FACTORS INVOLVED IN EXACERBATIONS OF DISEASE

The recurrent exacerbations of acute illness to which patients with chronic bronchitis are liable are a source of much disability. It is essential that everything be done to identify the factors responsible for these attacks, so that appropriate measures for prevention and control may be adopted. The surprising finding that antibacterial chemotherapy, while it reduces the duration of illness and thus shortens sickness absence, apparently does not affect the incidence of exacerbations or the natural history of chronic respiratory disease insofar as this is indicated by decline in the FEV₁ should not lead to the conclusion that infection is of no importance. Viral or mycoplasmal agents could still play a significant role. Much more must be known about their occurrence, particularly in the early stages of respiratory disease, inasmuch as there is increasing evidence that these agents are involved in a considerable proportion of exacerbations. Limitations in field techniques for identification of viral and mycoplasmal agents almost certainly lead to a current underestimation of their presence and role. It is difficult, however, to escape the conclusion reached by Fletcher that infection cannot be a major factor in the natural history of chronic bronchitis, since acute attacks of bronchitis do not necessarily influence the course of the disease. This important conclusion certainly needs confirmation through additional surveillance of stable groups of people.

FACTORS INVOLVED IN DECLINE IN VENTILATORY LUNG FUNCTION

In the few longitudinal studies in which this question has been examined, cigarette smoking, next to aging, has been found to be the most important determinant of the rate of FEV₁ decline. Neither occupational exposures to dusts nor respiratory infections appear to influence the rate of decline, but the volume of sputum produced during the first hour after rising from sleep, which again is mostly determined by cigarette smoking, has been shown to be related to the rate of decline.

Longitudinal studies of hospital or clinic patients have usually shown that the rate of decline in FEV₁ of these patients is approximately double that which would be expected in the general community of persons of the same sex, age, and smoking habits. Furthermore, exacerbations of disease in patients, as in more representative samples of the community, apparently play little part in the rate of decline. The FEV₁ may decline suddenly for no apparent reason. Having dropped, it may

remain at the lower level. It is clearly important to discover the reasons for these mystifying changes.

INTERVENTION TO ALTER THE NATURAL DISEASE COURSE

The use of antibiotics to alter the course of chronic bronchitis in patients early in its development has not been effective. It is possible that even in the Medical Research Council trial of chemotherapy the disease was too firmly established in the patients for antibiotic drugs to produce any real impact on its course. The use of antibiotic drugs earlier in the course of the disease might be more successful. On the whole, however, this seems unlikely. Furthermore, any suggestion of giving such drugs to persons with such minor symptoms as persistent cough and sputum would raise serious ethical objections. While the MRC findings certainly need to be confirmed in this country, there is little reason for much optimism.

A more promising form of intervention now being carried out by Reid in Britain consists of a controlled trial of antismoking propaganda in a group of highly motivated and intelligent civil servants who have certain respiratory symptoms and electrocardiographic abnormalities but who are otherwise well and working. Persuasion has been effective in changing the habits of half of those with the specified abnormalities. Some 60 percent have remained ex-smokers for 1 year or more. While the results of this trial will be awaited with interest, a similar attempt at intervention is clearly needed in the United States.

Legislation to reduce air pollution has already resulted in a remarkable reduction in pollution in Britain and a considerable reduction may be expected from measures being taken in the United States. The opportunity to measure what effects such legislation has on health in general and on the occurrence, progression, and outcome of respiratory disease in particular should not be missed. Similarly, improvements in industrial hygiene that have resulted in reduction of dust or fume demand that well-designed studies be conducted to assess the effects of these changes on human health.

CORRELATION OF CLINICAL AND PHYSIOLOGICAL CHANGES

Correlations of clinical findings with pathology in persons studied in epidemiological surveys are sparse. This is not surprising, since the problems of obtaining permission for autopsies in the general community are great; however, because the vast majority of persons in the United States die in hospitals, the problems should not be insuperable. A greater effort should be made by all who conduct surveys to ensure that competently performed examinations of the lungs are carried out at death on those who were part of a study population.

It is clear that we are far from understanding the complex interactions of factors that lead to disability and death from chronic respiratory disease, although clinical, epidemiological, and statistical studies have enabled us to form some idea of the complexity of such interactions. Although it has emerged as a very important and probably the most important factor, cigarette smoking is certainly not the only factor, and the way in which it interacts with other factors (infection, respiratory irritants, heredity, and constitution) requires much more study. Such studies should be coordinated with investigations into the mechanisms underlying the development and progression of chronic respiratory disease. The need for an

integrated attack on the problem through clinical, physiological, morphological, biochemical, immunological, and other means has been recognized in the current funding of Specialized Centers of Research by the National Heart and Lung Institute. Such an integrated attack should result in increased knowledge and understanding of chronic respiratory disease during the next decade and should enable us to reverse the present trends in mortality and disability through more effective prevention and control.

SUMMARY

During the past 20 years, much progress has been made in defining and classifying the components of chronic obstructive respiratory disease. The Ciba Conference on Terminology, Definitions, and Classification of Chronic Pulmonary Emphysema and Related Conditions;³⁷ the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases of the American Thoracic Society;¹⁰⁴ and the Committee on Cor Pulmonale of the World Health Organization³⁸ have established sound bases for the diagnosis of asthma, chronic bronchitis, and emphysema.

The practical measures for identifying persons in the community who have these chronic respiratory diseases have been developed by many groups of workers. They have been succinctly described by the British Medical Research Council's Committee on the Etiology of Chronic Bronchitis,⁴³ and, more recently, by the Committee on Standards for Epidemiologic Surveys in Chronic Respiratory Disease of the American Thoracic Society¹⁰⁴ in their respective publications on standardized methods for respiratory disease surveys. Standardized questions about respiratory symptoms, smoking habits, occupational and residential exposures, collection of sputum during the first half hour or hour after rising, and simple tests of ventilatory lung function (FEV and FVC) form the basis for any adequately conducted study. Additional tests may be added but should not be substituted.

Examination of the reproducibility and discrimination of these tests has led most workers to conclude that they are sufficiently good for epidemiological work. More recently, studies have shown that, as assessed by subsequent mortality rates, answers to questions about respiratory symptoms and measures of ventilatory lung function have considerable validity as epidemiological study indicators.

These methods have been applied to different types of populations. More surveys have been made of occupational groups than of the general population, though the number of these has been increasing during the past decade. In earlier epidemiological studies, adults alone were considered. More recently, in light of the realization that the genesis of chronic respiratory disease may occur early in life, children have received increasing attention. To date, the published work on children has been largely British and Japanese, but studies are in progress in the United States and other countries. Studies of children are of particular value for the light they shed on factors other than smoking that are involved in the etiology of respiratory disease.

Most studies have confirmed the initial observations that the most important factor in the natural history of chronic respiratory disease is smoking, particularly cigarette smoking. Prevalence, incidence, and remission of symptoms; level and decline over the years of ventilatory lung function; mortality from all causes and from respiratory diseases specifically--all of these suggest that there is a consistency in the findings about smoking that holds for no other factor.

In contrast, the relationships of general air pollution and of occupational exposures to chronic respiratory disease have been observed to be less consistent.

In the case of air pollution, it has been known for many years that episodes of exceptional pollution can cause appreciable mortality and morbidity. Much of this mortality and morbidity has no doubt occurred in persons already disabled with heart or lung diseases. The initiating effect of air pollution has been harder to establish. It now seems clear, particularly from the studies conducted in Britain on young people, that residence in polluted areas plays a significant part in the early development of chronic respiratory disease.

Assessment of the importance of occupational exposures has been plagued by the difficulty of allowing adequately for socioeconomic circumstances and for smoking. There is, however, a great deal of evidence pointing to the conclusion that coal miners and other workers in dusty occupations have an excess of chronic respiratory disease. Not only do the vital statistics and morbidity data indicate this, but surveys that have compared dust-exposed workers with other workers have nearly always shown consistently higher respiratory disease rates and lower lung function values in the dust-exposed groups. Two considerations have indicated that the role of dust exposure in the development of chronic respiratory disease is not as simple as it might appear at first sight. First, in some areas the differences between dust-exposed and nondust-exposed workers are small--indeed, in at least one area in this country there appeared to be no difference. Second, dust dosage, whether this is equated with the development of simple pneumoconiosis or with the number of years of underground or coal-face work, has not shown any very consistent relationship with either respiratory symptoms or level of lung function. This could reflect inadequate indices of dosage; it could result from an inability to allow adequately for differences in smoking habits between different exposure groups; or it could reflect selective factors, that is, those who have worked for long periods represent the healthier survivors of all the workers who originally started. It is difficult to avoid the conclusion that occupational dust exposures can contribute to chronic respiratory disease, sometimes substantially. Whether this contribution is by interaction with other factors or whether it is best described as initiation or aggravation can only be answered by well-designed experiments. It seems probable, too, that concentrations, and perhaps the composition, of dust in the working environment influence its effects on the respiratory tract.

Earlier studies established the relationship of *Haemophilus influenzae* and *Diplococcus pneumoniae* to chronic bronchitis, but there is still uncertainty as to the action of these organisms. During exacerbations the bacterial flora in the lower respiratory tract undergoes a quantitative rather than a qualitative change. This implies a change in the resistance of the host rather than a new infection or an alteration in bacterial virulence. Possibly such changes can be brought about by inhalation of irritants on the job or by general atmospheric pollution. It seems likely that they may often be precipitated by virus infections inasmuch as an increasing number of viruses have been shown to be associated with exacerbations of chronic respiratory disease. At present, however, a virus can be incriminated in only about half of all exacerbations. The reasons for the other exacerbations are as yet undetermined. The frequency of exacerbations is not reduced by antibacterial chemotherapy, though their duration may be reduced by up to one half with appropriate antibiotics. This is probably what would be expected if most exacerbations were precipitated by virus infections and subsequently underwent bacterial complication. A surprising finding has been that exacerbations of acute illness do not appear to influence the natural history of chronic respiratory disease, at least insofar as this is measured by the decline in FEV over the years. Perhaps this is

not a good index of the course of the disease. It is certainly desirable that the effect of exacerbations on the deterioration of other aspects of lung function should be assessed in addition to confirming this unexpected finding. It is difficult to believe that infection does not contribute to the development and course of chronic respiratory disease. Possibly the type of infection and perhaps its site of localization in the respiratory tract, particularly, are important factors that have not as yet been adequately studied. Possibly it is the treatment (or lack of it) that infections receive that is important. It may be that a "cold on the chest" that is ignored can lead to a greater decline in lung function than an attack of pneumonia that requires admission to hospital. All of these factors, plus the interaction of infection with other etiological factors, require further study.

The influence of hereditary and constitutional factors has received rather little study in epidemiological surveys to date, though the studies of twins have been an exception. The obvious importance of the discovery of α_1 -antitrypsin and its relationship to emphysema clearly indicates that more attention should be paid to these factors in the future. Allergy, at least insofar as this has been defined clinically, does not appear to be a very important factor in chronic respiratory disease; but bronchial reactivity, which may occur both in asthma and in chronic bronchitis, might provide a better measure of intermittent respiratory obstruction than the clinical indices that have been used to date. Measurement of immunoglobulins, which is becoming a practicable procedure, may also add precision to the diagnosis of the condition being investigated.

A number of miscellaneous factors have been linked with chronic respiratory disease in addition to the major ones mentioned above. Among these factors are infection of the gums and paranasal sinuses; exposure to poison gas; abdominal operations and the postoperative effects of anaesthesia; the influence of weather and climate; and a number of socioeconomic variables. Although relationships have been observed between these factors and chronic respiratory disease, the precise nature of those relationships remains undetermined and constitutes an area that demands--and deserves--further scrutiny.

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